UNIVERSIDAD COMPLUTENSE DE MADRID

FACULTAD DE MEDICINA
Departamento de Radiología y Medicina Física

TESIS DOCTORAL

Valor pronóstico de la radioterapia externa en el tratamiento multidisciplinar de pacientes con cáncer oligo-recurrente loco-regional

MEMORIA PARA OPTAR AL GRADO DE DOCTOR

PRESENTADA POR

Claudio Vicente Solé Pesutic

Director

Felipe Ángel Calvo Manuel

Madrid, 2015

UNIVERSIDAD COMPLUTENSE DE MADRID

FACULTAD DE MEDICINA
Departamento de Radiología y Medicina Física

VALOR PRONÓSTICO DE LA RADIOTERAPIA EXTERNA EN EL TRATAMIENTO MULTIDISCIPLINAR DE PACIENTES CON CANCER OLIGO-RECURRENTE LOCO-REGIONAL.

MEMORIA PARA OPTAR AL GRADO DE DOCTOR
PRESENTADA POR

Claudio Vicente Solé Pesutic

Bajo la dirección del Profesor Doctor

Felipe Ángel Calvo Manuel
Madrid, 2014

ISBN:

UNIVERSIDAD COMPLUTENSE DE MADRID

FACULTAD DE MEDICINA

DEPARTAMENTO DE RADIOLOGÍA Y MEDICINA FÍSICA

PROGRAMA DE CIENCIAS RADIOLÓGICAS

VALOR PRONÓSTICO DE LA RADIOTERAPIA EXTERNA EN EL TRATAMIENTO MULTIDISCIPLINAR DE PACIENTES CON CÁNCER OLIGO-RECURRENTE LOCO-REGIONAL.

TESIS PRESENTADA POR EL DOCTORANDO

CLAUDIO VICENTE SOLÉ PESUTIC

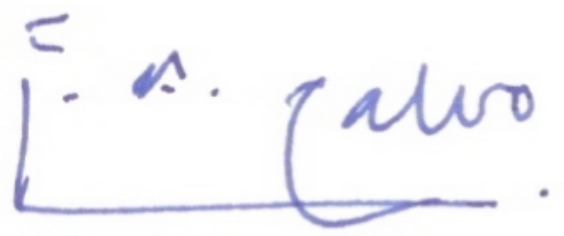
PARA OPTAR AL GRADO DE DOCTOR

DIRECTOR: FELIPE ANGEL CALVO MANUEL.

El Dr. D. Felipe Ángel Calvo Manuel, Jefe del Servicio de Oncología del Hospital General "Gregorio Marañón" y Catedrático de Oncología Radioterápica (Departamento de Radiología y Medicina Física) de la Universidad Complutense de Madrid.

CERTIFICA:

Que el trabajo titulado "**VALOR PRONÓSTICO DE LA RADIOTERAPIA EXTERNA EN EL TRATAMIENTO MULTIDISCIPLINAR DE PACIENTES CON CANCER OLIGO-RECURRENTE LOCO-REGIONAL"** ha sido llevado a cabo bajo mi dirección por D. Claudio Vicente Solé Pesutic, Licenciado en Medicina, especialista en Oncología Radioterápica, y reúne las condiciones exigibles para ser presentado como tesis para aspirar a la obtención del título de Doctor en Medicina. Para que conste y surta los efectos oportunos, firmo el presente certificado.



Prof. Felipe Ángel Calvo Manuel

Madrid, 5 de Mayo de 2014

A mi mujer, Filipa.

A mis padres, Claudio y Fresia.

A mis hermanos Bárbara, Vicente y Valentina.

AGRADECIMIENTOS:

Quiero agradecer en primer lugar a mi director de Tesis, el Profesor Dr. Felipe Ángel Calvo Manuel. Por su gran capacidad de trabajo, motivación, perseverancia y paciencia, y especialmente, por orientarme tanto en el ámbito profesional como personal. Debo señalar que sin su inmejorable guía esta tesis no se habría podido concretar.

Al Dr. Claudio Solé Barja, mi padre, por su entrega incondicional, por ser mi mayor y mejor ejemplo, por contagiarme de entusiasmo y por enseñarme todas las herramientas para desarrollarme no sólo como médico, sino que también como persona.

Al Dr. Mario Ramón Baeza, por ser mi primer mentor en Oncología, y por instruirme en la rigurosidad clínica, científica y metodológica.

Al Dr. Juan Solé Barja, por ser un gran líder, un trabajador incansable y por saber decirme lo que nadie más se atrevió a decir.

Al Dr. Sebastián Solé Zarhi, por su incesante labor asistencial, por su sincera amistad y su constante apoyo.

Al Profesor Dr. Hugo Marsiglia, por ser un referente académico, por su constante ayuda y por su generosidad desinteresada.

Al Servicio de Radioterapia del Instituto de Radiomedicina, en dónde me formé como especialista en Oncología Radioterápica, y al departamento de Oncología del Hospital General Universitario Gregorio Marañón y del Institut Gustave Roussy, en donde me perfeccioné como especialista e investigador.

A mis pacientes. Gracias por haberme enseñado tanto.

ÍNDICE:

Página

1. INTRODUCCIÓN

1. Introducción.

La predicción del pronóstico del paciente oncológico es esencial en la práctica clínica. A principios del siglo 20, Halsted [1] creía que los tumores sólidos se extendían contiguamente en una serie de etapas (desde el sitio del tumor primario, a través de los vasos linfáticos a órganos distantes) sucesivas temporales. El corolario de esta teoría, apoyado por investigaciones posteriores, fue que en el momento del diagnóstico inicial *(tumor-ganglios metástasis [TNM] etapa clínica) o después de la cirugía (TNM etapa patológica)*, el tamaño o la infiltración del tumor (T), el compromiso de los ganglios (N) linfáticos regionales y la presencia de metástasis a distancia (M) fueron índices de propagación de la enfermedad relativamente acertados para predecir el pronóstico de los pacientes. Es así como en 1953, el cirujano francés Pierre Denoix propuso a la Unión Internacional para el Control del Cáncer que estos tres factores se estandarizaran e integraran en un sistema pronóstico, que podría ser utilizado en todos los tumores sólidos, con una cierta adaptación por localización anatómica [2]. Esto dio origen al enfoque pronóstico más exitoso y duradero en oncología. Esta propuesta de un lenguaje común de factores pronóstico tumorales fue adoptado como el sistema de clasificación TNM, que se utiliza actualmente en todo el mundo (el sistema TNM ha sido sometido a siete revisiones [en los Estados Unidos]). Estos cambios han sido guiados por la Comisión Americana Unida contra el Cáncer (AJCC), que fue establecida en 1959 y que ha publicado una serie de revisiones en el manual AJCC de clasificación del cáncer [3].

El sistema de clasificación TNM es un modelo de grupos, en el que los factores pronósticos TNM se utilizan para crear un sistema exhaustivo de compartimentación excluyente, por lo que cada paciente se encuentra en un sólo

compartimiento, y los compartimientos se agrupan en contenedores mayores llamados etapas [4]. Se utiliza la supervivencia media de los pacientes en un determinado grupo para predecir la evolución oncológica de un nuevo paciente asignado en ese grupo. Por ejemplo, si un nuevo paciente se considera en el grupo (T1, N0, M0), después de 5 años la supervivencia de ese paciente se prevé que sea la misma que la supervivencia media de todos los pacientes que fueron evaluados y colocados en ese grupo hace 5 años. La utilidad del sistema deriva de su capacidad para ordenar los pacientes por probabilidad de supervivencia. Se trata de una herramienta clínica que puede ser utilizada para la selección terapéutica y para proporcionar una estimación pronóstica. Hay que tener presente que la cifra "5 años" es más bien referencial y convencional, ya que no se ajusta exactamente a la realidad de cada tumor en particular, pero sigue siendo un excelente referente de comparación.

Desde el primer Manual de clasificación de la AJCC, publicado en 1976 [5], hasta la séptima edición [3] se ha separado a los pacientes con tumores limitados a la estructura y órgano primario de los que presentan diseminación regional (metástasis ganglionares) [3]. Estos dos grupos de pacientes generalmente son tratados con intención curativa en contraste con los pacientes con metástasis a distancia, a los que generalmente no se les considera curables por los métodos actuales de tratamiento [6]. El estado de recurrencia o metástasis del cáncer se ha considerado que ocurre como evento tardío generalmente observado en la última etapa de la vida del paciente. Para la mayoría de los pacientes adultos con metástasis de tumores sólidos, el tratamiento para la enfermedad metastásica es la quimioterapia sistémica citotóxica, terapias biológicas y / o manipulación hormonal. En general estos pacientes no reciben un adecuado tratamiento local de

la enfermedad, debido a que se considera que las metástasis son con frecuencia, excesivamente numerosas y/ o presentan un extenso compromiso de órganos vitales [7] o que traducen un pronóstico ominoso por ser una enfermedad en etapa incurable y solo candidata a tratamientos paliativos. Desde este punto de vista, incluso si sólo un sitio de recurrencia o metástasis está presente, existe riesgo de diseminación por vía hematógena, lo que implica que la terapia local no puede erradicar todas las células cancerosas [6] o más bien que la terapia local no tendrá impacto en una enfermedad ya diseminada. La terapia sistémica puede entonces sólo prolongar la vida, en lugar de lograr el control definitivo de la enfermedad oncológica. Sin embargo, la evolución favorable de las terapias sistémicas ha obligado a cambiar este enfoque/paradigma nihilista.

Hellman y Weichselbaum proponen una noción alternativa en 1995, dando lugar a un cambio de paradigma en la conceptualización de la metástasis o recurrencia del cáncer (las etapas TNM no contemplan hasta la séptima edición una propuesta de categorización sistematizada de los pacientes con metástasis). Esta nueva noción de estado intermedio de metástasis se denominó oligometástasis [6]. En el momento del tratamiento de la lesión primaria, los pacientes con cáncer oligo-metastático pueden tener adicionalmente riesgo micrometástatico. Estas micrometástasis permanecen latentes por un período. Sin embargo, en su evolución suelen crecer y pueden ser detectados por tomografía axial computarizada, resonancia magnética, tomografía por emisión positrones y/ o aumento de los niveles de los marcadores tumorales. Debido al constante desarrollo en los métodos de imagen (resonancia magnética multiparamétrica y desarrollo de nuevos radiotrazadores para tomografía por emisión de positrones) , así como el de pruebas en base de fluidos y tejidos biológicos (biomarcadores

tumorales y determinación de células tumorales circulantes), es probable que se pueda identificar una población más ajustada de pacientes con oligometástasis y por lo tanto una fuente importante de oportunidades para la detección de tumores primarios en progresión y/o recurrencia , así como permitir el diagnóstico precoz de categorías oligometastática evolutivas susceptibles de tratamiento local curativo [6]. La evolución favorable de las terapias sistémicas ha permitido que este diagnóstico precoz de extensión se acompañe de acciones médicas útiles para mejorar las expectativas de vida del paciente, sino en duración en muchos casos, al menos en sobrevida libre de enfermedad clínica y/o oligosintomática, mejorando así la calidad de vida.

En este escenario, se ha sugerido que la evolución de la capacidad metastásica tiene estados intermedios en los que la propagación puede ser selectiva de órganos y finita en carga tumoral [7]. La implicación clínica de esta hipótesis indica que las formas localizadas de tratamiento del cáncer pueden ser eficaces en pacientes con oligometástasis. Por lo tanto, las terapias locales tales como la cirugía, radioterapia y ablación por radiofrecuencia de los sitios de recaída oncológica podrían mejorar la supervivencia de los pacientes a través de la remisión inducida por tratamientos que optimicen el control local. Por otro lado este mejor control local podría influir en un mejor efecto de las terapias sistémicas, las que actualmente tienen una limitada efectividad cuando deben enfrentar una carga tumoral total macroscópica [7].

La identificación de la categoría de oligometástasis (Figura. 1) representa un avance conceptual importante, pero mantiene incógnitas importantes por resolver. El estado de la lesión primaria de estos pacientes no tiene restricciones, a pesar de que se ha sugerido que los pacientes con lesiones primarias activas tienen peor

pronóstico que los pacientes con lesiones primarias controladas [7]. Se ha planteado que un tumor primario activo sigue siendo fuente de metástasis lo que se ha corroborado en numerosos estudios que muestran que un mejor control local se acompaña de una mejor sobrevida [7]. En los pacientes con oligometástasis sincrónicas (concepto originalmente descrito por Hellman y Weichselbaum) tanto el sitio del tumor primario como una o varias metástasis a distancia no están controladas. En esta categoría de pacientes, incluso si todos los sitios metastáticos fuesen tratados con una terapia local efectiva, el tumor primario no se controla y por lo tanto no se alcanza el objetivo de radicalidad terapéutica oncológica [8].

Niibe et al. [8-10] propuso una nueva aproximación para superar las limitaciones del modelo propuesto anteriormente. Este concepto, denominado oligo-recurrencia, es similar al concepto de oligometástasis. Sin embargo, agrega la dimensión de temporalidad de la metástasis y/o recurrencia. Las condiciones de oligo-recurrencia son: (i) una a varias metástasis recurrentes (normalmente una) en uno o varios órganos (habitualmente uno), (ii) sitio primario del cáncer controlado; (iii) una o varias metástasis/ recurrencias que pueden ser tratados con terapia local, y (iv) no hay otras metástasis a distancia/ recurrencias distintos de los de (iii). Este estado de oligo-recurrencia se muestra en la figura 1 y las diferencias entre oligometástasis y oligo-recurrencia se enumeran en la Tabla 1. Tal como se ha mencionado cabe destacar que en función de la temporalidad en la aparición de la metástasis se puede refinar aún más la estructura de la categorización. En oligo-recurrencia las metástasis son metacrónicas al diagnóstico del tumor primario, mientras que en oligometástasis son sincrónicas al diagnóstico de la lesión original [11]. Por otro lado si la recurrencia guarda relación con el sitio de la localización del primario/ drenaje linfático regional a distancia o ambos, se

denominan con los términos oligo-recurrencia loco-regional (local, regional o loco-regional), a distancia y mixta (Figura 2). Los conceptos de oligometástasis y oligo - recurrencia son actualmente algunas de las nociones de vanguardia más sugerentes en la biología del cáncer metastático y recurrente [11].

Figura 1. Espectro de presentaciones oligometastáticas y oligo-recurrentes en pacientes con cáncer de recto

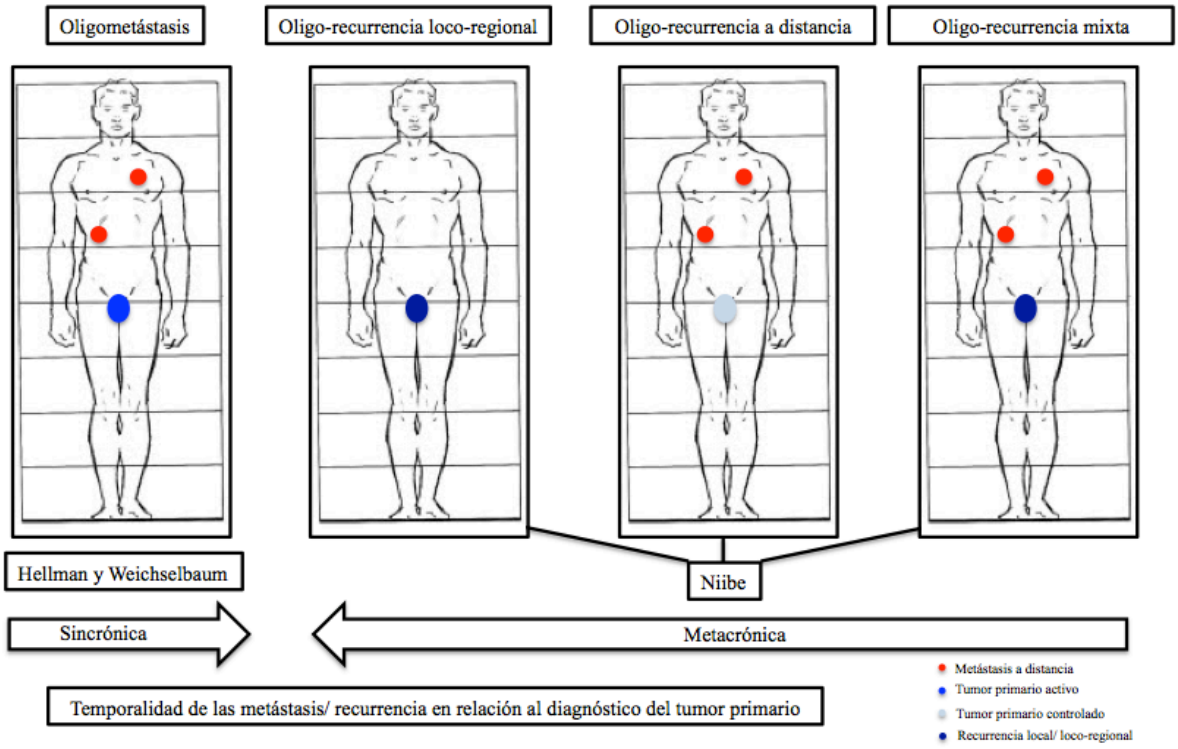


Tabla 1. Clasificación de oligometástasis y oligo-recurrencia

	Oligometástasis	**Oligo-recurrencia**
Referencia	Hellman y Weichselbaum	Niibe
Número de metástasis/ recurrencias	1 a varias (5)	1 a varias (5)
Temporalidad de las metástasis/ recurrencia en relación al diagnóstico del primario	Sincrónica	Metacrónica

Estos conceptos son ampliamente aceptados por los oncólogos, y se han comunicado numerosos informes de oligometástasis y oligo–recurrencia [7].

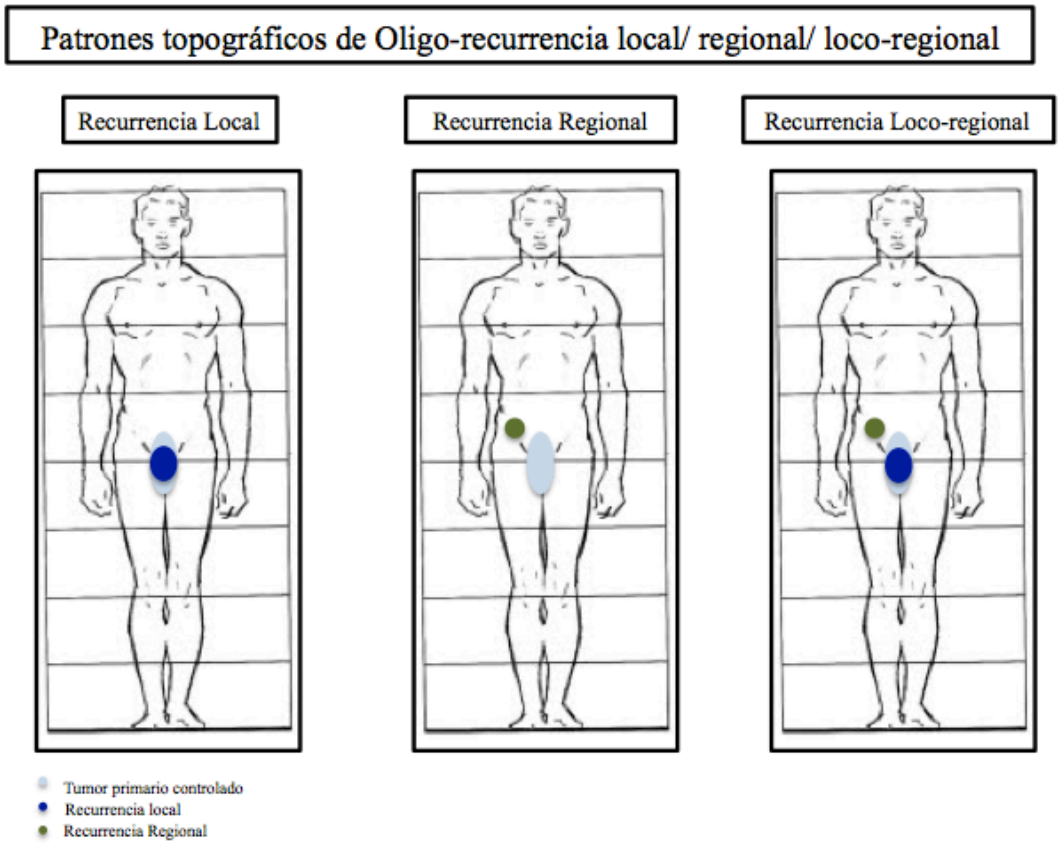
Niibe et al. identificó que el factor pronóstico más importante en pacientes con oligometástasis es el estado de la lesión primaria [11]. Este factor mantiene su valor pronóstico en los pacientes con oligo-recurrencia loco-regional y/o mixta en los que a pesar de que la lesión primaria está controlada, la recurrencia loco-regional guarda relación espacial y pronóstica con la extensión y características del tumor original. Sin embargo, este factor pronóstico decisivo, no está presente en el grupo de pacientes con oligo-recurrencia a distancia. Este es un aspecto trascendente con respecto a la terapia local. La terapia local es relativamente factible para el tratamiento de pocos, convencionalmente 1 a 5 focos metastáticos a distancia. Hasta la actualidad se han comunicado numerosas experiencias de resección quirúrgica y radioterapia estereotáctica ablativa de pacientes con oligometástasis y/ u oligo-recurrencias hepáticas [12-15], pulmonares [16-20] y suprarrenales secundarios de una gran variedad de sitios primarios [21-22], describiendo supervivientes a largo plazo en subgrupos de pacientes. Sin embargo, se requiere un seguimiento más maduro y un mayor número de pacientes para confirmar el potencial curativo de la radioterapia estereotáxica y otras técnicas de ablación no resectivos para este seleccionado grupo de pacientes.

Está bien documentado que el tratamiento de la lesión primaria (particularmente en estadios loco-regionalmente avanzados) y/ o recurrencia loco-regional es técnicamente difícil con terapia local (incluyendo la radioterapia, cirugía, y terapia ablativa de radiofrecuencia). Esto se debe fundamentalmente a que el componente loco-regional de la oligo-recurrencia a menudo implica metástasis macroscópicas en ganglios linfáticos regionales y/ o estructuras neuro-vasculares con extensión a

partes blandas y/o invasión de órganos adyacentes por contigüidad. Lo que hace aumentar el riesgo de daño a los tejidos normales al intentar cubrir todas las áreas anatómicas comprometidas.

La complejidad añadida de la extensión local del cáncer oligo-recurrente es la razón por la que se considera que la mayoría de los pacientes con oligo-recurrencia a distancia (exceptuando las lesiones de sistema nervioso central) tienen un pronóstico más favorable que los pacientes con oligo-recurrencia mixta y loco-regional [11]. Los pacientes con patrón de oligo-recurrencia loco-regional y mixto, tienen un pronóstico particularmente adverso, con escasas posibilidades terapéuticas (generalmente no se tratan con intención curativa) y por lo tanto mínimas posibilidades de supervivencia a largo plazo [23].

Figura 2. Patrones topográficos de oligo-recurrencia en pacientes con cáncer rectal



Es importante añadir que el pronóstico de los pacientes con oligometástasis y oligo-recurrencia es específico al tumor primario y a la localización metastásica. Esto se basa en el concepto de las múltiples etapas de progresión neoplásica (teoría de la semilla y el suelo) [24, 25]. La teoría de la semilla y el suelo sigue siendo una noción aceptada por la oncología y biología moderna [26-28]. Las interacciones de las células cancerosas con los órganos diana son muy dependientes y específicas a nivel de mutación de genes, expresión de genes y expresión molecular [26-28]. Las múltiples etapas de la progresión del cáncer indican que las células cancerosas en la lesión primaria no son monoclonales y tienen diferente potencial metastático [11].

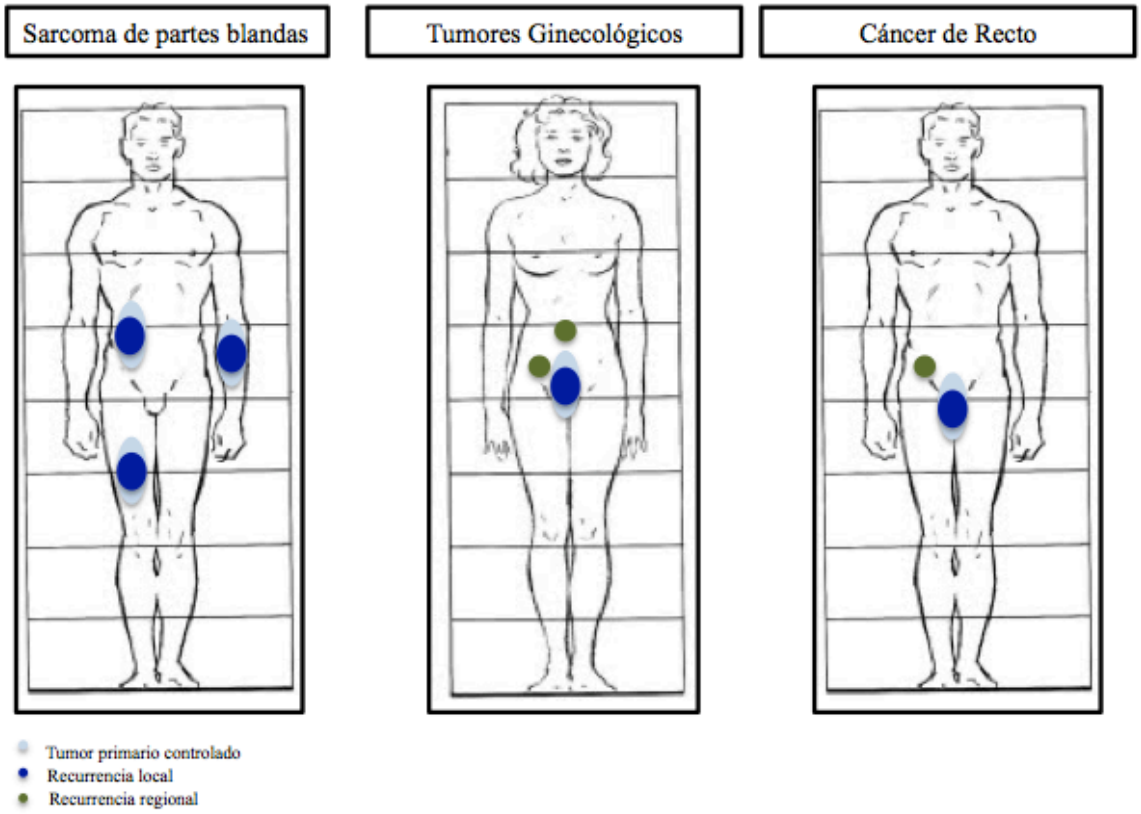
La teoría de la semilla y el suelo se adapta en el concepto de oligo-recurrencia. En pacientes con cáncer de pulmón de células no microcítico, la oligo-recurrencia se desarrolla a menudo sólo en el cerebro, o al menos como primer sitio de recidiva (oligo-recurrencia a distancia) [29]. En el cáncer de cuello uterino, la oligo-recurrencia a menudo afecta sólo a los ganglios para-aórtica (oligo-recurrencia regional) [30]. En el cáncer de recto, la oligo-recurrencia a menudo implica metástasis hepáticas y pulmonares (oligo-recurrencia a distancia), sin embargo la recidiva local en la región presacra le sigue en frecuencia (oligo-recurrencia local) [31].

Está descrito que el espectro de presentaciones englobadas bajo la categoría de oligo-recurrencia local, regional y loco-regional es muy amplio, sin embargo se ha identificado que un subgrupo seleccionado de pacientes podría beneficiarse de una abordaje terapéutico local intensivo [32-35].

Las mejoras logradas en los últimos 15 años en el tratamiento del cáncer incluyen la promoción del control local como objetivo esencial en el manejo de los tumores

rectales, ginecológicos y sarcoma de partes blandas. Se ha impulsado tanto el desarrollo de la técnica quirúrgica, como la secuenciación más favorable de esquemas de radioterapia y radio-quimioterapia en estrategias de tratamiento combinado. La evidencia publicada demuestra que se ha logrado reducir el riesgo de recidiva local después de la resección potencialmente curativa. Sin embargo, la oligo-recurrencia loco-regional aún constituye un evento clínico devastador para el subgrupo de pacientes con este patrón de progresión (cáncer de recto [5 al 15%], sarcoma de partes blandas [5-40%] y neoplasias ginecológicas [5-40%]) [36-40].

Figura 3. Representación esquemática de modelos anatómicos de oligo-recurrencia local, regional y loco-regional



En este grupo de pacientes la práctica clínica ha evolucionado desde la abstención terapéutica y/o radioterapia (quimio) paliativa hacia enfoques multimodales combinados [41-51].

Las guías publicadas el 2013 por la Red Nacional Integral del Cáncer (NCCN) sólo reconocen recomendaciones terapéuticas en oligo-recurrencia loco-regional de primarios rectales y oligo-recurrencia local de sarcoma de partes blandas. En la actualidad, la cirugía resectiva y la combinación concomitante de radio-quimioterapia son los pilares principales del tratamiento curativo. Numerosos estudios han informado que la radicalidad de la resección es el predictor más importante de la supervivencia [52-56]. Una resección completa con margen quirúrgico negativo es a menudo difícil de lograr debido a la proximidad o a la invasión de estructuras adyacentes. En este contexto, los enfoques multimodales, incluyendo estrategias de intensificación local y/o loco-regional deberían explorarse con objeto de mejorar los resultados de supervivencia y promover el control local [51, 57, 58].

Dada la baja incidencia de la oligo-recurrencia local y/ o loco-regional en la práctica clínica habitual, el diseño y ejecución de ensayos aleatorizados controlados que evalúen diferentes esquemas de tratamiento son difíciles de realizar, y por lo tanto son escasos los estudios de este tipo que se han comunicado hasta la fecha [59].

En este contexto, se han investigado nuevos factores pronósticos y resultados de supervivencia a largo plazo en un amplio grupo pacientes con oligo-recurrencia loco-regional tratados en instituciones académicas con cirugía resectiva seguida de radioterapia intraoperatoria con haz de electrones (RIO) administrada zonas de

alto riesgo (lecho quirúrgico post-resección y pre-reconstrucción) con o sin radioterapia externa con fotones (RTE).

La madurez evolutiva, el tamaño muestral de los distintos subtipos histológicos, la homogeneidad diagnóstica y de los componentes terapéuticos empleados en instituciones expertas en estrategias de rescate oncológico intensificado, convierten el presente análisis clínico-terapéutico en la experiencia oncológica más sistematizada y extensa de cáncer oligo-recurrente.

2. PACIENTES Y MÉTODOS.

2. 1. JUSTIFICACIÓN Y OBJETIVOS.

2.1.1. HIPÓTESIS DE TRABAJO.

En el momento actual no existe un tratamiento estándar para el abordaje de los pacientes con oligo-recurrencias loco-regionales por cáncer de recto, ginecológicos o sarcomas de partes blandas. La resección quirúrgica de máxima radicalidad es el tratamiento de elección, complementado (si es factible) por un tratamiento combinado de radioterapia externa con fotones y quimioterapia (radiosensibilizante basada en fluopirimidinas y/ o cisplatino) en casos seleccionados.

La secuencia óptima para conseguir el mejor índice terapéutico respecto a resultados de control local, supervivencia y tolerancia es debatida. Las instituciones proactivas en rescate de oligo-recurrencias optan por el tratamiento preoperatorio, con objeto de inducir la máxima regresión tumoral sin aumentar la toxicidad secundaria a los tratamientos. El tratamiento pre-operatorio permite también definir mejor el blanco (diana) radioterápico y disminuye el riesgo de implantabilidad de las células cancerosas post-resección. Las estrategias multidisciplinares de desarrollo e innovación terapéutica han evolucionado en dos direcciones:

1) Énfasis en terapias sistémicas: investigar la quimioterapia concomitante, explorando modelos de infusión basados en estudios farmacodinámicos, fluoropirimidinas orales (capecitabina [oligo-recurrencia rectal]), compuestos derivados del platino [cisplatino (oligo-recurrencia ginecológica)], antraciclinas [adriamicina (oligo-recurrencia de sarcoma de partes blandas)], compuestos derivados del gas mostaza (ifosfamida [oligo-recurrencia de sarcoma de partes blandas]) y nuevos citostáticos con propiedades radiopotenciadoras.

2) Incorporación de terapias locales: introducir técnicas de irradiación para incrementar el depósito de dosis efectiva sobre las áreas afectas por la oligo-recurrencia, con exclusión de los tejidos normales dosis-sensibles, mediante modificación del fraccionamiento de la dosis, sobreimpresión selectiva con radioterapia intraoperatoria o irradiación externa de alta adaptación dosimétrica.

El tratamiento quirúrgico exclusivo ha obtenido históricamente resultados de control loco-regional a 5 años entorno al 30 a 50%. Algunos centros expertos en abordaje radio-quirúrgico han utilizado la radioterapia intraoperatoria para intensificar el componente radioterápico mediante la sobreimpresión superselectiva del residuo de alto riesgo de cáncer con control quirúrgico. Se pretende optimizar el tratamiento oncológico integral mediante la minimización de la exposición de tejidos normales a la radiación (desplazamiento temporal de los órganos y estructuras dosis-sensibles no afectados por cáncer) y la selección ultra-precisa de la zona de tratamiento con control visual directo intraquirúrgico (máxima exactitud).

La utilización de radio-quimioterapia concomitante impulsa adicionalmente el control local en estos pacientes, evidenciando resultados aparentemente superiores al tratamiento quirúrgico exclusivo.

Nuestra hipótesis clínica explora si la inclusión de radioterapia externa dentro de un programa de cirugía resectiva y radioterapia intraoperatoria en pacientes con cáncer de recto, ginecológicos y sarcomas de partes blandas loco-regionalmente oligo-recurrentes, puede mejorar el control local, y promover la supervivencia a largo plazo sin comprometer la toxicidad crónica. La evidencia de que la radioterapia externa en tumores primarios aumenta significativamente el control local y en algunos casos la supervivencia, permite especular con un efecto similar

en pacientes con biología de cáncer oligo-recurrente (contribución a la escalada de dosis integral).

Para evaluar esta hipótesis se ha diseñado un estudio observacional-analítico que examina la experiencia clínico-asistencial en una cohorte retrospectiva de pacientes incluidos en un programa multi-institucional para el tratamiento de la oligo-recurrencia loco-regional utilizando cirugía, radioterapia intraoperatoria con electrones y quimioterapia adyuvante, con o sin radioterapia externa con fotones (y/ o radio-quimioterapia concomitante).

La hipótesis de trabajo del presente estudio plantea que los pacientes sometidos a radioterapia externa con fotones presentarán un control local superior, en comparación con la cohorte sin radioterapia externa.

Por tanto, esta teoría se puede sintetizar de la siguiente forma:

HIPÓTESIS NULA (H0): el control local actuarial a 5 años obtenido en los pacientes tratados con radioterapia externa con fotones, cirugía y radioterapia intraoperatoria, NO es significativamente superior al conseguido utilizando el esquema de rescate con cirugía y radioterapia intraoperatoria exclusiva.

HIPÓTESIS ALTERNATIVA (H1): el control local actuarial a 5 años obtenido en los pacientes tratados con radioterapia externa, con fotones cirugía y radioterapia intraoperatoria, es significativamente superior al conseguido utilizando el esquema con cirugía y radioterapia intraoperatoria.

2.1.2. OBJETIVOS DEL ESTUDIO.

Objetivo principal:

1. Evaluar la eficacia, en términos de control local, de un protocolo sistematizado de tratamiento en pacientes con cáncer oligo-recurrencia loco-regional (y/ o local y/o regional) utilizando radioterapia externa, cirugía y radioterapia

intraoperatoria.

Objetivos secundarios:

1. Analizar los resultados del protocolo integral multidisciplinar de tratamiento respecto a los parámetros clínico-evolutivos de mayor relevancia: supervivencia libre de enfermedad y supervivencia global.

2. Evaluar el efecto terapéutico sobre los resultados clínico-evolutivos y analizar el riesgo pronóstico.

3. Evaluar la tolerancia y factibilidad del programa multimodal de tratamiento de rescate, de forma integral y acumulativa.

2.2. METODOLOGÍA.

2.2.1. DISEÑO DEL ESTUDIO.

Se ha diseñado un estudio observacional-analítico, retrospectivo, no aleatorizado, de cohortes mixtas:

1. Una cohorte, que incluye los pacientes sometidos al programa institucional con radioterapia externa, cirugía y radioterapia intraoperatoria, objetivo del análisis del presente estudio (brazo experimental).

2. Una cohorte, constituida por pacientes sometidos a cirugía y radioterapia intraoperatoria (brazo control).

2.2.2. ÁMBITO.

INSTITUCIONES:

Modelo de oligo-recurrencia loco-regional de primario rectal y ginecológico:

Hospital General Universitario Gregorio Marañón.

Modelo de oligo-recurrencia local de sarcoma de partes blandas:

Hospital General Universitario Gregorio Marañón, Hospital Universitario Ramón y

Cajal y Cínica Universitaria de Navarra.

SERVICIOS MÉDICO -QUIRÚRGICOS CON IMPLICACIÓN CIENTÍFICO - ASISTENCIAL:

Oncología Radioterápica.

Oncología Médica.

Cirugía General y del Aparato Digestivo.

Cirugía Ortopédica y Traumatológica.

Ginecología y Obstetricia

Anestesia y Reanimación.

Radiología e Imagen Médica.

Anatomía Patológica.

Radiofísica Hospitalaria.

2.2.3. POBLACIÓN.

La población objetivo del estudio incluyó pacientes con el diagnóstico histológico confirmado de oligo-recurrencia loco-regional de tumores primarios de recto, ginecológicos y sarcoma de partes blandas, que fueran potencialmente candidatos a un tratamiento radical con resección quirúrgica y sobreimpresión con radioterapia intraoperatoria, seguida de quimioterapia adyuvante.

2.2. Metodología

2.2.3.1. Criterios de inclusión

2.2.3.2. Criterios de exclusión

2.2.4. Período de estudio

2.2.5. Descripción de variables

2.2.6. Análisis estadístico

3. Resultados.

Prognostic Impact of External-Beam Radiation Therapy in Patients treated with and without Extended Surgery and Intraoperative Electrons for locally recurent Rectal Cancer: 16-Year Experience in a Single Institution

Felipe A. Calvo, M.D., Ph.D., [1,2,6] Claudio V. Sole, M.D., Ph.D.c, [1-3,6] Pedro Alvarez de Sierra, M.D., Ph.D., [2,4] Marina Gómez-Espí, M.D., [1,5,6] Jose Blanco, M.D., [1,5,6] Miguel A. Lozano, M.D., [1,5,6] Emilio del Valle, M.D., [4,6] Marcos Rodriguez, M.D., [4,6] Alberto Muñoz-Calero, M.D., [4,6] Fernando Turégano, M.D., [4,6] Rafael Herranz, M.D., [1,2,5,6] Luis Gonzalez-Bayon M.D., Ph.D., [4,6] Jose Luis García-Sabrido, M.D., Ph.D., [2,4,6]

[1] Department of Oncology. Hospital General Universitario Gregorio Marañón. Madrid, Spain.
[2] School of Medicine. Complutense University. Madrid, Spain.
[3] Service of Radiation Oncology. Instituto de Radiomedicina. Santiago, Chile.
[4] Service of General Surgery. Hospital General Universitario Gregorio Marañón, Madrid, Spain.
[5] Service of Radiation Oncology. Hospital General Universitario Gregorio Marañón. Madrid, Spain.
[6] Institute of Research Investigation. Hospital General Universitario Gregorio Marañón. Madrid, Spain.

Running title: [Intraoperative radiotherapy for locally recurrent rectal cancer]

Keywords: Recurrent oligotopic rectal cancer; intraoperative radiotherapy; extended surgery; external beam radiation therapy

Corresponding author: Claudio V. Sole, M.D.
Hospital General Universitario Gregorio Marañon, Madrid, Spain.
C/ Doctor Esquerdo, 46 - 28007 Madrid.
Phone:+ (34) 91 586 85 99. Fax:+ (34) 91 426 93 89 Email: cvsole@uc.cl

The authors declare no potential and real commercial conflicts of interest.

Abstract

Purpose: To analyze prognostic factors associated with survival in patients after intraoperative electrons containing resective surgical rescue of locally recurrent rectal cancer (LRRC).

Methods and materials: From January 1995 to December 2011, 60 patients with LRRC underwent extended surgery [n=38; multiorgan (43%), bone (28%), soft tissue (38%)] or non-extended (n=22) surgical resection, including a component of intraoperative electron-beam radiation therapy (IOERT) to the pelvic recurrence tumor bed. Twenty-eight (47%) of these patients also received external beam radiation therapy [EBRT (range, 30.6-50.4 Gy)]. Survival outcomes were estimated using the Kaplan-Meier method, and risk factors were identified by univariate and multivariate analyses.

Results: Median follow-up was 36 months (range, 2-189), the 1- 3-, and 5-year rates for locoregional control (LRC) and overall survival (OS) were 86, 52, 44%; and 78, 53, 43%, respectively. On multivariate analysis R1 resection, EBRT at the time of pelvic re-recurrence, no tumor fragmentation and non-lymph node metastasis retained significance with regard to LRR. R1 resection and no tumor fragmentation showed a significant association with OS after adjustment for other covariates.

Conclusions: EBRT treatment integrated for rescue, resection radicality, and not involved fragmented resection specimens are associated with improved LRC in patients with locally recurrent rectal cancer. Additionaly, tumor fragmentation could be compensated by EBRT. Present results suggest that a significant group of patients with LRRC may benefit from EBRT treatment integrated with extended surgery and IOERT.

Introduction

Although the improvements achieved in the treatment of rectal cancer over the last 15 years, such as total mesorectal excision and radio/radiochemotherapy regimens, have reduced the risk of local recurrence after potentially curative resection, the incidence of pelvic failure still averages 5 to 15% [1-3]. Locally recurrent rectal cancer (LRRC) is a broad disease category, and it has been reported that some patients may benefit from intensive local therapy [4-5]. Clinical practice has shifted from non-intervention or palliative (chemo) radiation to more intensive multimodal approaches combined with intended radical surgery [6-7]. Several studies have reported that radicality of the resection of LRRC is the most significant predictor of improved survival [8-10]. Nonradical resections are associated with 5-year survival rates between 0 and 15%, whereas this rate increases to 52% after radical resections [8]. A complete negative margin resection is often questionable to be achieved due to close proximity or proven invasion into adjacent unresectable structures. Therefore, multimodal approaches including additional local therapies might be implemented to further improve patient outcomes and optimize local control and survival [6, 10-11]. Given the rarity of LRRC, randomized trials evaluating various treatment regimens are difficult to conduct, and to our knowledge few studies of this nature have been published to date [12]. In this context, we investigated outcomes and novel risk factors for an expert single-institution group of patients with LRRC treated with extended or radical intent non-extended surgery followed by intraoperative radiotherapy electron-beam radiation therapy (IOERT) in high-risk areas (post-resection and pre-reconstruction) with and without external-beam radiation therapy (EBRT).

Materials and Methods

Patient selection criteria

This study was approved by the institutional review board and was performed in compliance with hospital ethics and clinical practice guidelines. Subjects with pathologically confirmed LRRC without extra-pelvic disease were offered to participate in a developmental institutional treatment protocol that consisted of rescue surgery and IOERT to the tumor bed area at risk for residual disease. Consideration for surgical approach, perioperative EBRT and adjuvant chemotherapy (CT) was discussed upon individualized bases. Tumor Board considered for multimodal recommendation: initial treatment characteristics, location, tumor resectability and clinical status of patients. Prospectively collected hospital records of 60 patients treated for LRRC between January 1995 and December 2011 were retrospectively reviewed. Patients were assessed at baseline by digital examination when possible, abdomen and pelvic computed tomography (CT) scan, pelvic magnetic resonance imaging (MRI) and chest X-ray. A classification system based on CT scan and MRI was used in the evaluation of the extent of infiltration on the pelvic sidewall and the topographic site of local recurrence (LR) [13]. Five groups were defined to classify the extent of infiltration on the pelvic side-wall: F0 [n=2 (3%)]: no evidence of contact with the pelvic side-wall; F1 [n=17 (28%)]: extent of contact less than a quarter of pelvic side-wall; F2 [n=7 (12%)]: contact was less than half circumference; F3 [n=16 (27%)]: contact more than half circumference; F4 [n=18 (30%)]: involvement of bony structures or small bowel. Topographic LR was classified into one of the following regions: (1) posterior: predominantly midline, in contact with the sacral bone [n=32 (53%)]; (2) posterolateral: laterally located, near to or invading the piriform muscle, in

contact with the sacral bone [n=20 (33%)]; (3) anterior-lateral: in association with anterior located organs, pelvic sidewalls or along the iliac vessels [n=8 (14%)]. Patient and treatment characteristics are listed in Table 1. Compared treatment-based cohorts of patients were well balanced between patients receiving extended surgical resection [n=38 (63%)] and non-extended surgical resection [n=22 (37%)]. We found that patients in the extended surgery group had more advanced tumors with greater extension involvement to the pelvic sidewall than patients in the non-extended surgical group.

Treatment details

Details of EBRT, concomitant and adjuvant CT followed standards previously described [14]. Perioperative EBRT (Preoperative [n=19]; postoperative [n=9]) was delivered with megavoltage equipment (6 to 15 MV) and began within 24 hours of CT administration (n=27, 96%). Conformal three-dimensional radiotherapy was planned; fields were arranged taking into account doses delivered to normal tissues during radiotherapy for primary tumor. However, no specific dose–volume constraints were indicated by the treatment protocol. A total median dose of 45 Gy [(range, 45 to 50.4 Gy (1.8 Gy/5 d/wk)] for non-previously irradiated (n=22) patients and 30.6 Gy [(range, 21.6 to 30.6 Gy (1.8 Gy/5 d/wk)] for previously irradiated patients (n=6), was prescribed to the isodose line which covered the planning target volume (PTV) to obtain a homogeneity ranging between **+/-** 5% of the prescribed dose. PTV was defined as LR (gross target volume [GTV]) plus 2cm of radial margin for preoperative EBRT and surgical tumor bed (clinical target volume [CTV]) plus 2cm of radial margin for postoperative EBRT patients. Chemotherapy concomitant schedule consisted of

oral fluoropirimidine (Tegafur), 1.2 g/d1-17-28. Patients had a 4-week rest after surgery and then could receive additionally adjuvant CT (n=30, 50%). Extended surgical (n=38) procedures [4-6 weeks before or after perioperative treatment] consisted of lateral extended endopelvic resection (LEER) [n=6 (16%)], posterior exenteration [n=6 (16%)], total pelvic exenteration [n=9 (23%)], sacrectomy [n=6 (16%)] and sacroexenteration [n=11 (29%); posterior, n=3; total, n=8]. Non-extended surgical procedures were associated to low anterior resection [n=8 (36%)], ultra low anterior resection [n=3 (14%)] and abdominoperineal resection [n=11 (50%)] together with LR resection. The institutional IOERT program is performed in a non-dedicated linear accelerator with outpatient radiotherapy activity. After surgery and before pelvic reconstruction, 10 to 15 Gy (median, 12.5 Gy) were delivered in a single fraction to a one (n=53, 88%) or two-field (n=7, 12%) PTVs, using a median energy of 12 MeV (range, 6 to 18 MeV). Intraoperative margin status was assessed using frozen pathologic sections, patients with R0 resections received an IOERT dose of 10 to 12.5 Gy and patients with R1 resections received 15 Gy. Beveled (15-45º) Lucite circular applicators (size range, 5 to 15 cm) were adjusted to collimate the target surface air gap, allowing dosimetric adaptation and uniform dose distribution. Computed-tomography guided treatment has been available since 2008 [15]. Table 2 shows macroscopic and microscopic histological characteristics and their relationship with IOERT technical parameters.

Follow-up and toxicity evaluation

All patients were scheduled to be followed according to the institutional protocol every 3 months after treatment completion for the initial 3 years and every 6 months for 3 additional years thereafter. Patients were restaged 4 weeks after RT

(before surgery) and routinely every 6 months with CT scan of the abdomen and pelvis. Assessment of surgical complications was done according Clavien-Dindo classification [16]. Acute and toxicities were evaluated according to Radiation Therapy Oncology Group/ European Organization for Research and Treatment of Cancer score [17].

Statistical analysis

Data collected was analyzed by using SPSS (version 19.0) statistical software. The primary endpoint of the analysis was loco-regional control (LRC). Secondary endpoints were OS, disease-free survival (DFS) and distant metastases-free survival (DMFS). The Kaplan-Meier method was used to estimate the probabilities LRC, OS, DFS and DMFS. Potential associations were assessed in univariate and multivariate analyses by using the Cox proportional hazards model (two-sided p test ≤ 0.05). Adjustment was performed for factors significant on univariate analysis (two-sided p test < 0.10).

Results

Median follow-up time for the entire cohort of patients was 36 months (range, 2-189). Median follow-up time for surviving patients was 77 months (range, 21-189). No patients were lost of follow-up. Twenty patients remained alive at the time of analysis. Of the 40 deceased patients, 33 (88%) died from proven cancer progression, 3 (5%) died from treatment toxicity, and 4 (7%) died from causes unrelated to their cancer or treatment. Twenty-eight patients had a second LRR (47%), 28 out of the original 60 patients (47%) developed distant metastases [sites of distant metastases including: lung (n=12), liver (n=9), peritoneum (n=5), bone (n=1) and brain (n=1)], and 15 (25%) patients had a synchronous local and

distant progression. Eight out of the 28 (29%) patients who had a second LRR were rescued with a second surgical procedure, achieving 3 long-term survivors (49, 90 and 170 months).

Overall survival for the study population at 1-, 3- and 5- years was 78, 53 and 43%, respectively [Figure 1]. Univariate Cox proportional hazard analyses showed that R1 resection (p=0.004) was associated with inferior OS. No tumor fragmentation was associated with a trend towards superior overall survival (p=0.07) [Table 3]. After adjustment for other covariates, R1 resection and no tumor fragmentation showed a significant association with OS [Table 4]. The 1- 3-, and 5-year rates of LRC were 86%, 52%, and 44%, respectively [Figure 1]. On univariate analysis, not receiving EBRT (5-year LRC= 56.2% vs. 32.0%, p=0.02) and R1 resection (5-year LRC= 55.7% vs. 19.0%, p=0.02) were at a significantly higher risk of LRR [Table 3; Figure 2A-2B]. Patients without tumor fragmentation [Figure 2C] and age > 55 had a lower risk of LR relapse [Table 3]. We found on multivariate analysis that R1 resection, EBRT integrated at the time of LRR, non-metastatic lymph nodes and no tumor fragmentation retained significance [Table 4]. We then evaluated patients with and without radical resection separately. For the subset with R0 resection (n=38), patients who did not receive EBRT experienced a significantly higher risk of local relapse in univariate analysis [HR 3.23 (CI95%1.0-9.96); p=0.05] [Figure 2D]. Alternatively, for the subset with R1 resection (n=22), univariate analysis did not showed that patients not receiving EBRT had an increased risk for a second local relapse [HR 2.28 (CI95% 0.74-7.02); p=0.15]. When tumor fragmentation was evaluated in patients with and without EBRT to the pelvic LRR, we found that only for the subset with tumor fragmentation (n=26), not receiving EBRT showed worse LRC [HR 2.84

(CI95%1.08-8.04); Figure 2E]. For patients without tumor fragmentation (n=34) this analysis did not reach statistical significance [HR 1.84 (CI95% 0.61-5.51); p=0.28]. In regard to patients with extended surgical resection (n=38), not receiving EBRT increased the risk of LRR [HR 0.05 (CI95% 0.03-0.67); p=0.014]. Finally, we found no difference in the LRR rate among patients with extended surgical resection and non-extended surgery [HR 1.15, (CI95% 0.55-2.44); p=0.71] [Figure 2F]. DMFS and DFS at 1-, 3- and 5-years, were 85 and 52 and 43%; and 81, 46 and 37%, respectively [Figure 1]. Univariate analyses showed that no tumor fragmentation was associated with a lower risk of DMFS [Table 3]. After adjustment for other covariates, no tumor fragmentation retained a favourable significance [Table 4]. In regard to DFS, no tumor fragmentation was the only factor significantly associated with DFS on multivariate analysis.

Causes of acute and chronic toxicity were estimated as multifactorial [18]. Overall 25 patients (42%) had grade ≥ 3 acute toxicity [gastrointestinal fistula (n=4, grade 3), soft tissue abscess (n=1, grade 3), wound infection (n=3, grade 3; n=2; grade 5), peripheral neuropathy (n=4, grade 3; n=1, grade 4), cardiac (n=4, grade 3; n=1, grade 5) and pulmonary (n=5, grade 3)]. Twelve patients (20%) developed chronic toxicity ≥ 3 [gastrointestinal (n=4, grade 3; n=2, grade 4), neurologic (n=3, grade 3; n=3, grade 4)]. Overall treatment mortality was 5% [n=3 (n=2, wound infection-sepsis; n=1, cardiac)]. No long-term death from treatment occurred. In regard to overall perioperative complications, we found that patients treated with extended surgery had higher rates of perioperative complications than patients treated with non-extended surgery [73.7% (n=28) vs. 45.5% (n=10); p=0.03], longer median time (minutes) of surgery [365 (145-750) vs. 260 (100 vs.465); p=0.02], longer median time (days) in the intensive care unit [2 (0-18) vs.

0 (0 vs. 2); p=0.004] and longer median time (days) of hospitalization [17 (1-156) vs. 10 (1-50); p=0.005]. In relation to perioperative mortality no difference was found [7.8% (n=3) vs. 0% (n=0); p=0.18)] [Table 1].

Discussion

Our relevant findings can be summarized as follows. First, we found that extended surgical resection compensates for adverse LR features. Second, we found that not adding EBRT to surgery and IOERT in patients with LRRC was significantly associated with a decreased risk of LRC. Interestingly, this maintained significance when patients with radical resection and tumor fragmentation were analyzed separately. Finally, we found that patients with no tumor fragmentation had a decreased probability of LR, DF and overall mortality and that nonradical resection patients had lower rates of LRC and OS. Although the number of studies assessing patients with LRRC rescued with surgery, IORT and EBRT is limited the major results reported in the present article [5-Year LRC (44%) and OS (43%)] are comparable with reported literature [5-Year LRC (30-75%) and OS (20-50%)] [6-11]. Haddock et al. [11] reported the largest institutional expert experience with IOERT for the rescue of recurrent colorectal cancer (n=607). Although detailed data on the site of recurrence and rescue are not provided, outcome was more favorable for recurrence in the colon than in the rectum (5-year survival 34% vs. 28%, p = 0.07). Kusters et al [10] analyzed 170 patients with LRRC who underwent multimodality treatment with preoperative CRT, elective radical surgery, and IOERT. The worst outcomes were seen in presacral recurrences [28% complete resections and 19% 5-year survival (p = 0.03)]. The most favorable outcomes were observed for anastomotic LRRC, with 77% R0 resections and 60% 5-year survival

(p = 0.04). Consistently, we also found that patients with non-radical resections had worse overall outcomes than patient with radical resections. Even more, patients with non-radical resections treated without EBRT had worse LRC than those who did received EBRT treatment. In a previous report [19] we evaluated the feasibility and long-term outcome of surgery combined with IOERT in patients with recurrent oligotopic extrapelvic cancer (n=28). With a median follow-up of 39 months, we found that LR was significantly affected by microscopic cancer in more than 50% of specimen fragments (38% vs. 9%, p = 0.02). In the current analysis, no tumor fragmentation was associated with an improved chance of LRC, DMFS and OS. In a subset analysis, patients with tumor fragmentation not receiving EBRT had a decreased probability of LRC. To this end, several studies have shown that pelvic reirradiation with a low total dose of EBRT is acceptably tolerated, with moderate rates of late toxicity and may help promote pelvic control [13]. In our report, patients being re-irradiated (n=7) were not associated with worse survival outcomes, probably due to the fact that 5 out of 7 had R0 resections, thus making it difficult to detect an advantage among patients without reirradiation (n=21). Valentini et al. [13] reported in patients with LRRC who had previously received pelvic EBRT, a 5-year overall survival of 39%, despite 87.4% of patients having sidewall involvement disease [35% R0 resections, 64% were alive at 5-years. Our finding that perioperative EBRT to LRRC patients was associated with improved outcomes is consistent with prior studies [13, 20]. Pacelli et al. [20] reported in a subset analysis of LRRC patients with potentially curative resection (R0–R1), that preoperative chemoradiotherapy improved 5-year OS (44.6 vs. 25.8%, p=0.012). However, data regarding the optimal treatment sequence and the contribution of an external beam radiation therapy (EBRT) component in this clinical scenario

remains to be elucidated.

In regard to treatment related toxicity, the acceptable tolerance and rate of postsurgical complications suggests that a multimodality approach with an extended surgical component for LRRC is feasible with tolerable risks and without prohibitive long-term side effects.

We acknowledge several limitations of our study. First, the population was heterogeneous, having been treated over 16-years and receiving different treatment combinations. Although we did observe a significant association between EBRT treatment and LRC after adjustment for several potential confounding factors, we certainly acknowledge the presence of a selection bias for patients referred for radiation therapy to a higher dose. A systematic method of follow-up, including imaging, would be optimal to evaluate patterns of failure after radiation therapy. Although, given the prospective nature of this analysis, consistent homogeneous imaging did not occur in a proportion of patients. Therefore, a significant number of patients with distant only recurrence may not have undergone optimal imaging of the pelvis at the time of recurrence. Finally, it must be emphasized that systemic therapy plays an important role in the management of LRRC. Up-front chemotherapy followed by either switch/continuation maintenance or observation in different combinations with local therapy should be tested in the scenario of a clinical trial if possible.

In conclusion, we found that LRRC patients that received EBRT and IOERT could be treated safely and had improved rates of LRC on both univariate and multivariate analysis. We also found that among patients with radical-resections and no tumor fragmentation experienced the largest benefit with EBRT treatment. Although, a level of adverse prognostic features (non-radical resections) might be

compensated by the addition of EBRT. Our results suggest that a subgroup of patients with LRRC could benefit from intensive local treatment to the LR.

Figure 1. Kaplan-Meier curves for all 60 patients for overall survival (A), disease-free survival (B), local-regional control (C), and distant metastasis-free survival (D).

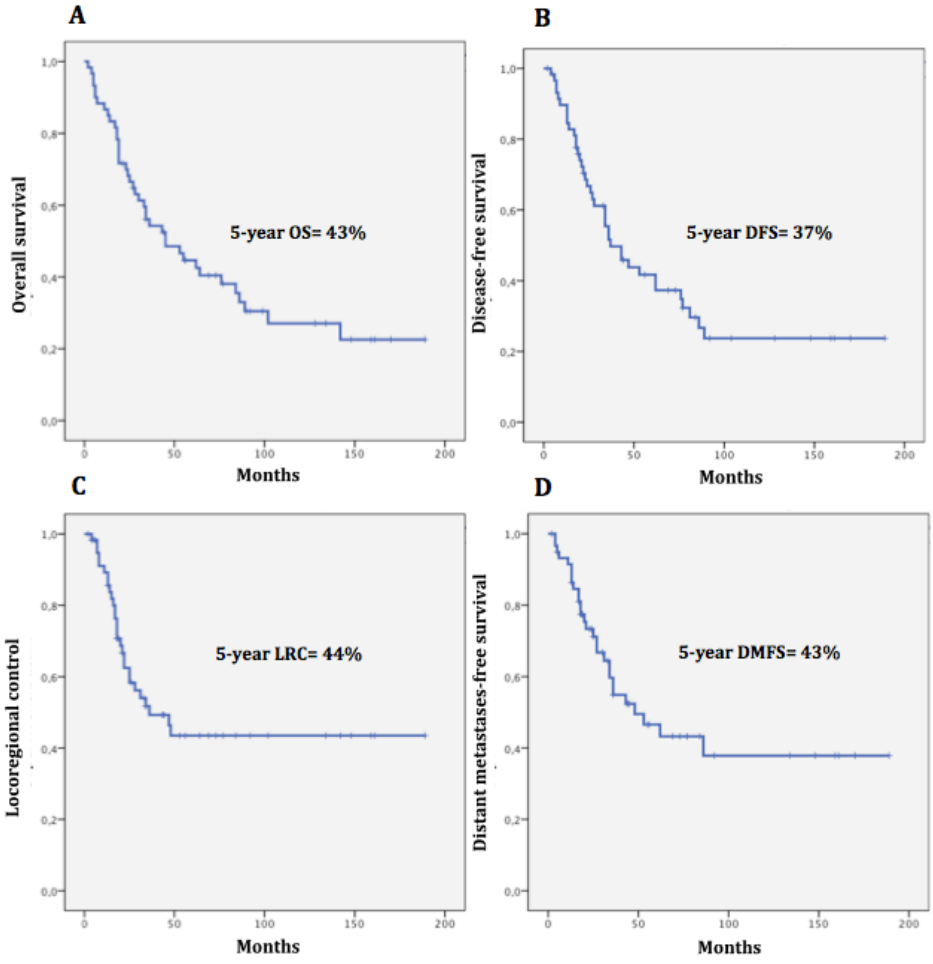


Figure 2. Locoregional control according to EBRT to the recurrent tumor (A), margin status (B), tumor fragmentation (C), EBRT to the recurrent tumor in R0 patients [n=38] (D), EBRT to the recurrent tumor in patients with tumor fragmentation [n=26] (E), and surgical (standard/ extended) resection (F)

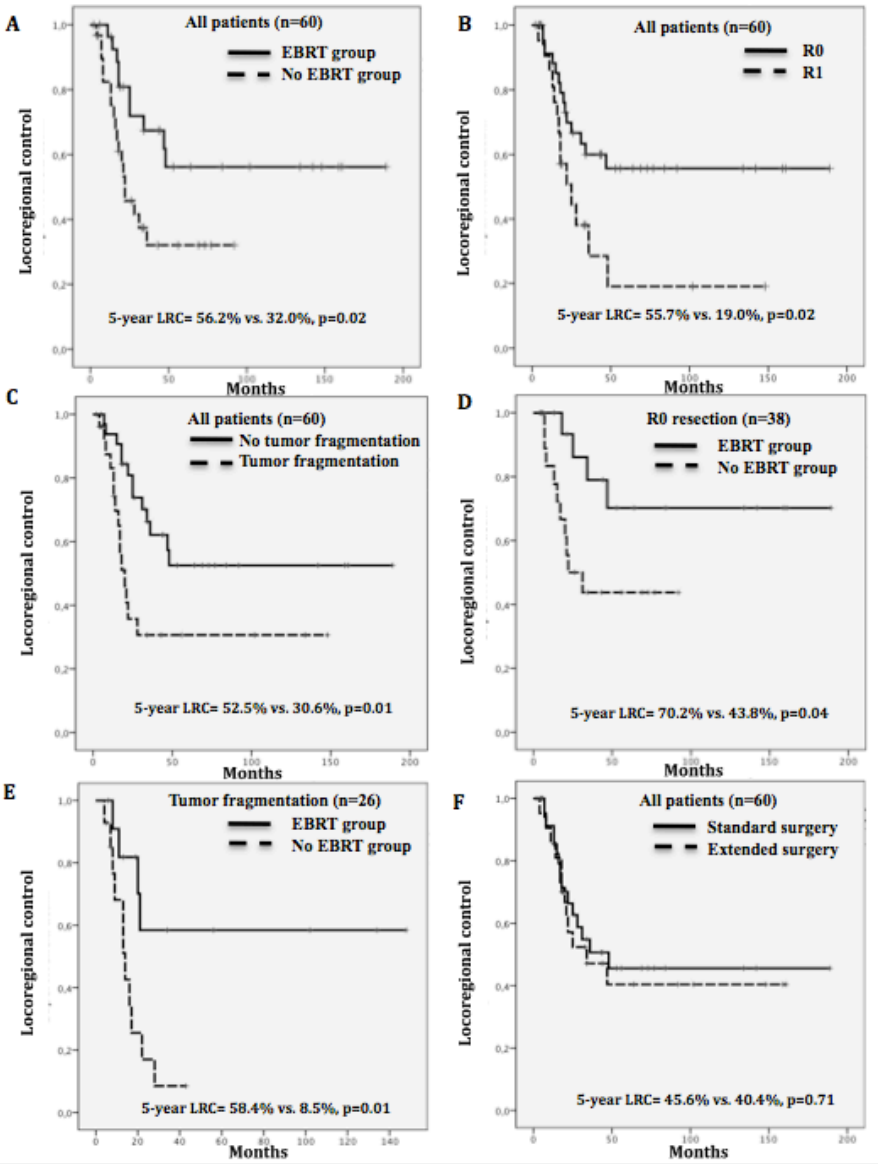


Table 1. Patient, tumor and treatment characteristics

Characteristics	All patients n=60 (%)	Extended surgery N=38 (%)	Non-extended surgery n=22 (%)	P-value
Patient variables				
Median age (range)	55.7 (35-79)	57.9 (35-73)	54.2 (35-79)	0.63
Gender **Male/ female**	33 (55) / 27 (45)	21/17	12/10	0.96
Karnofsky performance status **≥ 90/ < 90**	22 (37)/ 38 (63)	14/ 24	8/ 14	0.97
Median interval (months) from primary to LR (range)	27.2 (3-158)	26.1 (3-98)	28.1 (5-158)	0.89
Macroscopic tumor variables				
Extent of infiltration of the recurrence on the pelvic sidewall **F0/ F1/ F2/ F3/ F4**	2 (3)/ 17 (28)/ 7 (12)/ 16 (27)/ 18 (30)	0/ 0/ 4/ 16/ 18	2/ 17/ 3/ 0/ 0	<0.001
Pelvic relapse topography **Posterior/ posterolateral/ antero-central**	32 (53)/ 20 (33)/ 8 (14)	23/ 11/ 4	9/ 9/ 4	0.33
Maximum recurrent tumor diameter **≥ 5 cm vs. < 5 cm**	23 (38)/ 37 (62)	17/ 21	6/ 16	0.25
Median recurrent tumor size (range)	4.5 (2-9)	4.8 (2-9)	4.1 (2-6)	0.35
Tumor fragmentation **Yes vs No**	26 (43)/ 34 (57)	18/ 20	8/ 14	0.41
Microscopic tumor variables				
Initial primary tumor histological grade **I-II vs. III**	52 (87)/ 8 (13)	3/ 35	5/ 17	0.10
Margin status **R0 vs. R1**	38 (63)/ 22 (37)	25/ 13	13/ 9	0.61
Recurrent tumor lymph node status **Metastatic vs. Non-metastatic**	8/ (13)/ 52 (87)	4/ 34	4/ 18	0.40
Surgical variables				
Multiorgan resection **Yes vs. No**	26 (43)/ 34 (57)	26/ 12	0/ 22	<0.001
Bone resection **Yes vs. No**	17 (28)/ 43 (72)	17/ 21	0/ 22	0.001
Soft tissue resection **Yes vs. No**	23 (38)/ 37 (62)	23/ 15	0/ 22	<0.001
Radiation therapy and chemotherapy variables				
Adjuvant chemotherapy initial primary tumor **Yes vs. no**	36 (60)/ 24 (40)	25/ 13	11/ 11	0.23
EBRT for initial primary tumor **Yes vs. no**	30 (50)/ 30 (50)	20/ 18	10/ 12	0.59
Adjuvant chemotherapy for recurrent tumor **Yes vs. no**	30 (50)/ 30 (50)	21/ 17	9/ 13	0.13
EBRT for recurrent tumor **Yes vs. no**	28 (47)/ 32 (53)	15/ 23	13/ 9	0.14

Acute toxicity ≥ 3				0.44
Gastrointestinal fistula				
Soft tissue abscess	4 (7)	2	2	
Wound infection	1 (2)	1	0	
Peripheral neuropathy	5 (8)	3	2	
Cardiac	5 (8)	3	2	
Pulmonary	5 (8)	2	3	
	5 (8)	3	2	
Chronic toxicity ≥ 3				0.23
Gastrointestinal	6 (10)	6	4	
Peripheral neuropathy	6 (10)	6	4	
Perioperative mortality				0.18
Yes vs. no	3 (8)/ 0 (0)	3	0	

[+]Chi-square or Mann-Whitney test

EBRT, external-beam radiation therapy; Multiorgan resection (≥ 2 pelvic organs) [posterior exenteration (n=6), total pelvic exenteration (n=9), sacroexenteration (n=11)]; Bone resection [laterally extended endopelvic resection [LEER] (n=1), sacrectomy (n=6), sacroexenteration (n=11)]; Soft tissue resection [LEER (n=6), sacrectomy (n=6), sacroexenteration (n=11)].

Table 2. Correlations between macroscopic/microscopic pathology characteristics and IOERT technical parameters.

Pathology/ IOERT	**Surgical specimens**	**Applicator size**	**IOERT dose (Gy)**	**IORT energy (MeV)**
		Median/ range	**Median/ range**	**Median/ range**
Total number of fragments				
1	34	6/ 5-10	12.5/ 10-15	10/ 6-15
2	10	6/ 5-12	12.5/ 10-15	12/ 6-18
3	8	7/5-12	12.5/ 10-15	12/ 6-18
4	5	8/6-12	12.5/10-12.5	12/6-12
5-6	3	7/5-10	12.5/12.5-15	15/10-18
Tmax size (cm)				
2.0-3.0	33	6/ 5-9	12.5/ 10-15	9/ 6-15
3.1-5.0	11	6/ 5-12	12.5/ 10-15	12/ 6-15
5.1-9.0 [+]	16	8/ 7-12	12.5/ 10-15	12/ 6-18

[+] 1- field PTV, 53 patients; 2-field PTV, 7 patients.

Table 3. Univariate analyses of associations between the patient, tumor, treatment, and pathologic characteristics and survival

Parameter	Variable	Locoregional control			Distant metastases free survival			Disease free survival			Overall survival		
		HR	CI 95%	P value	HR	CI 95%	P value	HR	CI 95%	P value	HR	CI 95%	P value
Patients													
Age (years)	***≤ 55***	1.0			1.0	0.35-1.60	0.46	1.0			1.0	0.47-1.64	0.68
	> 55	0.47	0.22-1.0	**0.05**	0.75			0.74	0.39-1.40	0.74	0.87		
Gender	***Male***	1.0			1.0	0.55-2.45	0.71	1.0	0.67-2.41	0.46	1.0		
	Female	0.91	0.43-1.92	0.81	1.16			1.27			0.86	0.46-1.62	0.65
Karnofsky performance status	***> 90***	1.0			1.0	0.61-2.39	0.48	1.0	0.67-2.50	0.44	1.0		
	≤ 90	1.08	0.50-2.29	0.85	1.22			1.29			1.47	0.75-2.86	0.26
Macroscopic surgical specimen													
Extent of infiltration on the pelvic sidewall	**F0-F2**	1.0			1.0			1.0			1.0		
	F3-F4	1.06	0.50-2.22	0.88	1.12	0.53-2.37	0.77	1.15	0.61-2.17	0.87	1.13	0.60-2.11	0.71
Pelvic relapse topography	**Posterior**	1.0			1.0			1.0			1.0		
	Posterolateral	2.01	0.86-4.49	0.10	2.16	0.86-4.83	0.10	1.84	0.83-3.63	0.10	1.51	0.77-2.96	0.23
	Anterolateral	0.88	0.26-3.15	0.88	0.77	0.22-2.67	0.68	0.62	0.26-2.28	0.62	0.63	0.21-1.85	0.41
Recurrent tumor size	***> 5***	1.0			1.0			1.0			1.0		
	≤ 5	0.67	0.32-1.42	0.29	0.77	0.35-1.71	0.53	0.64	0.33-1.26	0.20	0.68	0.35-1.30	0.24
Recurrent tumor Fragmentation	***Yes***	1.0			1.0			1.0			1.0		
	No	0.38	0.18-0.82	**0.01**	0.31	0.14-0.66	**0.002**	0.52	0.28-1.0	**0.05**	0.56	0.3-1.05	**0.07**
Microscopic surgical specimen													
Primary tumor histologic grade	***I-II***	1.0			1.0			1.0			1.0		
	III	1.71	0.65-4.52	0.28	1.78	0.73-4.39	0.24	1.86	0.82-4.25	0.14	1.49	0.66-3.38	0.34
Recurrent tumor Margin status	***R0***	1.0			1.0			1.0			1.0		
	R1	2.28	1.08-4.82	**0.03**	1.83	0.82-4.11	0.14	1.83	0.95-3.53	**0.07**	2.55	1.36-4.80	**0.004**
Recurrent tumor Lymph node	***Metastatic***	1.0			1.0			1.0			1.0		
	Non-metastatic	0.16	0.02-1.16	**0.07**	0.53	0.16-1.76	0.29	0.56	0.19-1.56	0.27	0.61	0.22-1.72	0.35
Surgery													
Extended Surgery	***Yes***	1.0			1.0			1.0			1.0		
	No	0.87	0.41-1.83	0.71	0.95	0.44-2.02	0.89	0,78	0.40-1.48	0.44	0.82	0.43-1.54	0.54
Multiorgan resection	***Yes***	1.0			1.0			1.0			1.0		
	No	0.89	0.40-1.97	0.78	0.73	0.34-1.54	0.41	0.71	0.01-5.21	0.74	0.81	0.42-1.56	0.53
Vascular resection	***Yes***	ND											
	No												
EBRT and CT Treatment													
Primary tumor EBRT treatment	***Yes***	1.0			1.0			1.0			1.0		
	No	0.79	0.38-1.68	0.55	0.93	0.44-1.96	0.85	0.91	0.48-1.69	0.75	0.73	0.39-1.38	0.33
Primary tumor Adjuvant CT	***Yes***	1.0			1.0			1.0			1.0		
	No	1.04	0.49-2.21	0.91	1.67	0.73-3.81	0.22	1.1	0.53-2.1	0.93	0.79	0.41-1.47	0.45
Recurrent tumor EBRT treatment	***Yes***	1.0			1.0			1.0			1.0		
	No	2.40	1.10-5.21	**0.03**	1.07	0.51-2.25	0.86	1.30	0.69-2.44	0.43	1.35	0.72-2.55	0.35
Recurrent tumor Adjuvant CT	***Yes***	1.0			1.0			1.0			1.0		
	No	1.86	0.85-4.05	0.12	1.29	0.61-2.75	0.51	1.15	0.61-2.17	0.66	1.16	0.61-2.19	0.66

Table 4. Factors associated with locoregional control, distant metastases-free survival, disease-free survival and overall survival in multivariate analyses

Parameter	Variable	Locoregional control			Distant metastases free survival			Disease free survival			Overall survival		
		HR	CI 95%	P value	HR	CI 95%	P value	HR	CI 95%	P value	HR	CI 95%	P value
Tumor fragmentation	***Yes*** ***No***	1.0 0.49	0.23-0.95	**0.05**	1.0 0.35	0.16-0.75	**0.007**	1.0 0.54	0.29-1.0	**0.05**	1.0 0.48	0.25-0.91	**0.02**
Margin status	***R0*** ***R1***	1.0 2.09	1.04-4.53	**0.05**	-	-	-	-	-	-	1.0 2.90	1.51-5.57	**0.001**
Lymph node	***Metastatic*** ***Non-metastatic***	1.0 0.18	0.05-0.72	**0.03**	-	-	-	-	-	-	-	-	-
Recurrent tumor RT treatment	***Yes*** ***No***	1.0 0.42	0.19-0.95	**0.04**	-	-	-	-	-	-	-	-	-

Multivariate analysis was redone and was carried out backwise with pre-assigned p values of > 0.05 controlling step removal.

References.

[1]. Heald RJ, Moran BJ, Ryall RDH, et al. Rectal cancer: the Basingstoke experience of total mesorectal excision, 1978–1997. Arch Surg. 1998;133:894–9.

[2]. Sauer R, Liersch T, Merkel S, et al. Preoperative versus postoperative chemoradiotherapy for locally advanced rectal cancer: results of the German CAO/ARO/AIO-94 randomized phase III trial after a median follow-up of 11 years. J Clin Oncol. 2012;30:1926-33.

[3]. van Gijn W, Marijnen CA, Nagtegaal ID, et al. Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer: 12-year follow-up of the multicentre, randomised controlled TME trial. Lancet Oncol. 2011;12:575-82.

[4]. Wanebo HJ, Antoniuk P, Koness RJ, et al. Pelvic resection of recurrent rectal cancer: technical considerations and outcomes. Dis Colon Rectum. 1999; 42:1438–1448.

[5]. Hellman S, Weichselbaum RR. Oligometastases. J Clin Oncol. 1995; 13:8–10.

[6]. Roeder F, Goetz JM, Habl G, et al. Intraoperative Electron Radiation Therapy (IOERT) in the management of locally recurrent rectal cancer. BMC Cancer. 2012; 12: 592.

[7]. Hahnloser D, Nelson H, Gunderson LL, et al. Curative potential of multimodality therapy for locally recurrent rectal cancer. Ann Surg. 2003; 237:502–508.

[8]. Dresen RC, Gosens MJ, Martijn H, et al. Radical resection after IORT-containing multimodality treatment is the most important determinant for outcome in patients treated for locally recurrent rectal cancer. Ann Surg Oncol. 2008; 15:1937–1947.

[9]. Wells BJ, Stotland P, Ko MA, et al. Results of an aggressive approach

to resection of locally recurrent rectal cancer. Ann Surg Oncol. 2007;14:390–395.

[10]. Kusters M, Dresen RC, Martijn H, et al. Radicality of resection and survival after multimodality treatment is influenced by subsite of locally recurrent rectal cancer. Int J Radiat Oncol Biol Phys. 2009; 75:1444–9.

[11]. Haddock MG, Miller RC, Nelson H, et al. Combined modality therapy including intraoperative electron irradiation for locally recurrent colorectal cancer. Int J Radiat Oncol Biol Phys. 2011;79:143–50.

[12]. Braendengen M, Tveit KM, Berglund A, et al. Randomized phase III study comparing preoperative radiotherapy with chemoradiotherapy in nonresectable rectal cancer. J Clin Oncol. 2008; 26: 3687-94

[13]. Valentini V, Morganti A, Gambacorta MA, et al. Preoperative hyperfractionated chemoradiation for locally recurrent rectal cancer in patients previously irradiated to the pelvis: A multicentric phase II study. Int J Radiat Oncol Biol Phys. 2006; 64: 1129-1139.

[14]. Gunderson LL, Willett CG, Calvo FA, et al. editors. Intraoperative irradiation. Techniques and results. 2nd ed. Springer New York: Humana Press; 2011.

[15]. Pascau J, Santos Miranda JA, Calvo FA, et al. An innovative tool for intraoperative electron beam radiotherapy simulation and planning: description and initial evaluation by radiation oncologists. Int J Radiat Oncol Biol Phys. 2012; 83:287-295.

[16]. Clavien PA, Barkun J, de Oliveira ML, et al. The Clavien-Dindo classification of surgical complications: five-year experience. Ann Surg. 2009; 250:187-96.

[17]. Cox JD, Stetz J, Pajak TF. Toxicity criteria of the Radiation Oncology Group (RTOG) and the European Organization for Research and Treatment of Cancer

(EORTC). Int J Radiat Oncol Biol Phys. 1995; 31:1341–1346.

[18]. Azinovic I, Calvo FA, Puebla F, et al. Long-term normal tissue effects of intraoperative electron radiation therapy (IOERT): late sequelae, tumor recurrence, and second malignancies. Int J Radiat Oncol Biol Phys. 2001; 49: 597–604.

[19]. Calvo FA, González ME, González-San Segundo C, et al. Surgery and intraoperative electron radiotherapy in recurrent or metastatic oligotopic extrapelvic cancer: long-term outcome. Eur J Surg Oncol. 2012; 38: 955-61.

[20]. Pacelli F, Tortorelli A, Rosa F, et al. Locally recurrent rectal cancer: prognostic factors and long-term outcomes of multimodal therapy. Ann Surg Oncol. 2010; 17: 152–162.

External-Beam Radiation Therapy After Surgical Resection and Intraoperative Electron-Beam Radiation Therapy for Oligorecurrent Gynecological Cancer: Long-Term Outcomes

C.V. Sole, M.D., [1-3,7] F.A. Calvo, M.D., Ph.D., [1,2,7] M.A. Lozano, M.D., [1,4,7] L. Gonzalez-Bayon M.D., Ph.D., [5,7] C. Gonzalez-Sansegundo, M.D., [1,4,7] A. Alvarez, M.D., [4,7] S. Lizarraga, M.D, [6,7] J.L. García-Sabrido, M.D., Ph.D., [2,5,6]

[1] Department of Oncology. Hospital General Universitario Gregorio Marañón. C/ Doctor Esquerdo, 46 - 28007 Madrid, Spain.
[2] School of Medicine. Complutense University. C/ Ciudad Universitaria 28040, Madrid, Spain
[3] Service of Radiation Oncology. Instituto de Radiomedicina. C/ Americo Vespucio Norte, 1314-76003 Santiago, Chile.
[4] Service of Radiation Oncology. Hospital General Universitario Gregorio Marañón. C/ Doctor Esquerdo, 46 - 28007 Madrid, Spain.
[5] Service of General Surgery. Hospital General Universitario Gregorio Marañón. C/ Doctor Esquerdo, 46 - 28007 Madrid, Spain.
[6] Department of Gynecology. Hospital General Universitario Gregorio Marañón. C/ Doctor Esquerdo, 46 - 28007 Madrid, Spain.
[7] Institute of Research Investigation. Hospital General Universitario Gregorio Marañón. C/ Doctor Esquerdo, 46 - 28007 Madrid, Spain.

Short title: [IOERT for oligorecurrent gynecological cancer]

Keywords: [surgery, intraoperative radiotherapy, oligorecurrent gynecological cancer, external-beam radiation therapy]

Corresponding author: Claudio V. Sole, M.D. Hospital General Universitario Gregorio Marañon, Madrid, Spain. C/ Doctor Esquerdo, 46 - 28007 Madrid. Phone:+ (34) 91 586 85 99. Fax:+ (34) 91 426 93 89 Email: cvsole@uc.cl

Abstract

Purpose: To analyze prognostic factors in patients treated with external-beam radiation therapy (EBRT), surgical resection and intraoperative electron-beam radiotherapy (IOERT) for oligorecurrent gynecological cancer (ORGC).

Methods: From January 1995 to December 2012, 61 patients with ORGC [uterine cervix (52%), endometrial (30%), ovarian (15%), vagina (3%)] underwent IOERT (12.5 Gy (range, 10-15 Gy)] and surgical resection to the pelvic (57%) and paraaortic (43%) recurrence tumor bed. Twenty-nine (48%) patients also received external beam radiation therapy [EBRT (30.6-50.4 Gy)]. Survival outcomes were estimated using the Kaplan-Meier method, and risk factors were identified by univariate and multivariate analyses.

Results: Median follow-up time for the entire cohort of patients was 42 months (range, 2-169). Ten-year rates for overall survival (OS) and locoregional control (LRC) were 17 and 65%, respectively. On multivariate analysis no tumor fragmentation [HR 0.22; p=0.03], time interval from primary tumor diagnosis to loco-regional recurrence (LRR) < 24 months [HR 4.02; p=0.02] and no-EBRT at the time of pelvic recurrence [HR 3.95; p=0.02] retained significance with regard to LRR. Time interval from primary tumor to LRR < 24 months [HR 2.32; p=0.02] and no-EBRT at the time of pelvic recurrence [HR 3.77; p=0.04] showed a significant association with OS after adjustment for other covariates.

Conclusions: External-beam radiation therapy at the time of pelvic recurrence, time interval for relapse ≥ 24 months and not multi-involved fragmented resection specimens are associated with improved LRC in patients with ORGC. As suggested from the present analysis a significant group of ORGC patients could potentially benefit from multimodality rescue treatment.

Introduction

Historically a clinical state of metastasis termed 'oligometastases' has referred to restricted tumor metastatic capacity [1]. The implication of this concept is that local cancer treatments have a curative potential in a proportion of patients with metastases [1]. Conversely, up to one third of patients with gynecologic oligorecurrence have a rescue opportunity [2]. Long-term survival is rare (5-year overall survival 5%) for patients with pelvic sidewalls involvement, pelvic or paraaortic lymph node recurrence treated with standard salvage therapy [3]. Oligorecurrent gynecological cancer (ORGC) encompasses a broad disease category, consistently it has been reported that some patients may benefit from intensive local therapy [4-6]. Clinical practice of expert institutions has shifted from non-intervention or palliative treatment to more intensive multimodal approaches [7-13]. Successful salvage treatment is highly dependent on the extent of radicality of the resection [13]. Due to close proximity or proven tumor invasion into adjacent unresectable structures a complete negative resection margin is often questionable to be achieved. Therefore, a combined approach including additional local therapies could improve local control and survival [4-13]. To the best of our knowledge, no randomized trials evaluating different treatment regimens have been published to date. In this context, we investigated outcomes and novel risk factors for a group of patients with ORGC with pelvic sidewall or paraaortic isolated lymph node recurrence treated with surgical resection and intraoperative electron-beam radiation therapy (IOERT) in high-risk areas (post-resection and pre-reconstruction) with or without external-beam radiation therapy (EBRT).

Materials and Methods

Patient selection criteria

Treatment protocols were in compliance with hospital ethics and clinical practice guidelines. Subjects with pathologically confirmed ORGC with pelvic sidewall or paraaortic isolated lymph node recurrence (no other extra-pelvic disease) and Karnofsky score ≥ 70 were offered to participate in a developmental institutional treatment program that consisted of extended surgery, EBRT and IOERT to the tumor bed area at risk for residual disease. Tumor Board considered for surgical approach and adjuvant chemotherapy (CT) recommendation: initial treatment characteristics, location, tumor resectability and clinical status of patients. All (n=61) patients were offered to participate in the institutional EBRT plus IOERT program, but 32 (52%) elected not to consent (patients that did not consent EBRT had greater concerns related to re-treatment toxicity or issues related to treatment efficacy). Two treatment strategies were operational along the period: 29 (48%) patients were treated according to a research protocol that consisted of EBRT, surgery and IOERT with or without adjuvant chemotherapy (EBRT group). The remaining 32 patients were treated with surgery plus IOERT, but without EBRT (non-EBRT group) and served as the control cohort. Prospectively collected hospital records of patients treated for ORGC between January 1995 and December 2012 were retrospectively reviewed. Patients were assessed at baseline by physical and gynecological examination, abdomen and pelvic computed tomography (CT) scan, pelvic magnetic resonance imaging (MRI) and chest X-ray. Patient and treatment characteristics are listed in Table 1. Compared treatment-based cohorts of patients were balanced between patients with pelvic [n=35 (57%)] and paraaortic LR [n=26 (43%)].

Treatment details

Details of EBRT, concomitant and adjuvant CT followed standards previously described [13]. Perioperative EBRT (Preoperative [n=14]; postoperative [n=15]) was delivered with megavoltage equipment (6 to 15 MV) and begun within 24 hours of CT administration (n=25, 85%). Conformal three-dimensional radiotherapy for EBRT was planned; fields were arranged taking into account doses delivered to normal tissues during radiotherapy for primary tumor. However, no specific dose–volume constraints were indicated by the treatment protocol. A total median dose of 45 Gy [(range, 45 to 50.4 Gy (1.8 Gy/5 d/wk)] for non-previously irradiated (n=16) patients and 30.6 Gy [(range, 21.6 to 30.6 Gy (1.8 Gy/5 d/wk)] for previously irradiated patients (n=13), was prescribed to the isodose line which covered the planning target volume (PTV) to obtain a homogeneity ranging between **+/-** 5% of the prescribed dose. PTV was defined as LR (gross target volume [GTV]) plus 2cm of radial margin for preoperative EBRT and surgical tumor bed (clinical target volume [CTV]) plus 2cm of radial margin for postoperative EBRT patients. Chemotherapy concomitant schedule consisted of bolus intravenous cisplatin (75 mg/m2/d1 and d5, Qw4 x 2) or none (ovarian recurrence).

Patients had a 4-week rest after surgery and then could receive additionally adjuvant CT (n=24, 39%). Surgical procedures (4-6 weeks before or after perioperative treatment) consisted for pelvic recurrence of anterior exenteration with lateral extended endopelvic resection (LEER) (n=1 [3%]), LEER with vascular en bloc resection of the local recurrence (n=5 [14%]), LEER alone (n=11 [31%]), anterior exenteration (n=5 [14%]), posterior exenteration (n=3 [9%]), total pelvic exenteration (n=7 [20%]) and posterior sacroexenteration, (n=3 [9%]). For

paraaortic LR surgical resection consisted of transperitoneal regional lymphadenectomy only (n=9 [26%]) or associated with vascular (n=2 [8%]) or soft tissue resection (n=15 [58%]). The institutional IOERT program is performed in a non-dedicated linear accelerator with outpatient radiotherapy activity. After surgery and before pelvic reconstruction, 10 to 15 Gy (median, 12.5 Gy) were delivered in a single fraction to a one (n=42, 69%) or two-field (n=19, 31%) PTVs, using a median energy of 12 MeV (range, 6 to 18 MeV). Intraoperative margin status was assessed using frozen pathologic sections, patients with R0 resections received an IOERT dose of 10 to 12.5 Gy and patients with R1 resections received 15 Gy. Bevelled (15-45º) Lucite circular applicators (size range, 5 to 12 cm) were adjusted to collimate the target surface air gap, allowing dosimetric adaptation and uniform dose distribution. Computed-tomography guided IOERT treatment has been available since 2008 [14]. Table 2 shows macroscopic and microscopic histological characteristics and their relationship with IOERT technical parameters.

Follow-up and toxicity evaluation

All patients were scheduled to be followed according to the institutional protocol every 3 months after treatment completion for the initial 3 years and every 6 months for 3 additional years thereafter. Patients were restaged 4 weeks after RT (before surgery) and routinely every 6 months with CT scan of the abdomen and pelvis. Assessment of surgical complications was done according Clavien-Dindo classification [15]. Acute and late toxicities were evaluated according to Radiation Therapy Oncology Group/ European Organization for Research and Treatment of Cancer score [16].

Statistical analysis

Data collected was analyzed by using SPSS (version 19.0) statistical software. The primary endpoint of the analysis was loco-regional control (LRC). Secondary endpoints were OS and disease-free survival (DFS). The Kaplan-Meier method was used to estimate the probabilities LRC, OS, DFS and DMFS. Potential associations were assessed in univariate and multivariate analyses by using the Cox proportional hazards model (two-sided p test ≤ 0.05). Adjustment was performed for factors significant on univariate analysis (two-sided p test ≤ 0.05).

Results

Median follow-up time for the entire cohort of patients was 42 months (range, 2-169). Median follow-up time for surviving patients was 56 months (range, 3-169). No patients were lost of follow-up. Twenty-seven patients remained alive at the time of analysis. Of the 34 deceased patients, 27 (79%) died from proven cancer progression, 1 (3%) died from treatment toxicity, and 6 (18%) died from causes unrelated to their cancer or treatment. Sixteen patients had a second LRR (26%), 21 out of the original 61 patients (34%) developed distant metastases [sites of distant metastases including: lung (n=10), liver (n=6) and peritoneum (n=5); 7 (11%) patients had a synchronous local and distant progression] and the total recurrence rate was 49% [30 out of 61 patients, median time to any recurrence was 19 months (range, 2-78)]. Six out of the 16 (38%) patients who had a second LRR were re-rescued with a second surgical procedure, achieving 3 long-term survivors (39, 45 and 56 months).

Overall survival for the study population at 5-, and 10- years was 42 and 17%, respectively [Figure 1A]. On univariate analysis, time interval from primary tumor diagnosis to LR < 24 months (p=0.01), and not receiving EBRT to the LR (p=0.02)

were associated with inferior OS [Table 3]. We found on multivariate a time interval from primary tumor diagnosis to LR < 24 months and not receiving EBRT at the time of LRR retained significance [Table 4].

Disease-free survival at 5- and 10-years was 44 and 28%, respectively [Figure 1B]. Univariate analyses showed that a time interval from primary tumor diagnosis to LR < 24 months (p=0.007), paraaortic recurrence site (p=0.05), primary tumor grade 3 (p=0.02) and not receiving EBRT to the LR (p=0.05) were associated with a higher risk of overall metastases [Table 3]. After adjustment for other covariates, primary tumor diagnosis to LR < 24 months and not receiving EBRT to the LR, retained significance in regard to DFS [Table 4].

The 5- and 10-years rates of LRC were 65 and 65%, respectively [Figure 1C]. Univariate Cox proportional hazard analyses showed that time interval from primary tumor diagnosis to LR < 24 months (p=0.03), squamous carcinoma histology (p=0.03) and not receiving EBRT to the LR (p=0.007) were associated with inferior LRC. No tumor multi-fragment involvement (fragments involved by tumor on pathology report) was associated with a superior likelihood of LRC (p=0.02) [Table 3]. We found no difference in the LRR rate among patients with R0 resection and R1 resection [HR 1.65, (p=0.15]. After adjustment for other covariates, time interval from primary diagnosis to LR < 24 months, not receiving EBRT to the LR and no tumor fragmentation showed a significant association with LRC [Table 4]. We then evaluated patients with and without radical surgery separately. For the subset with R0 resection (n=32), patients without tumor multi-fragment involvement experienced a significantly lower risk of local relapse in univariate analysis [HR 0.13 (CI95% 0.01-0.96); p=0.05]. Alternatively, for the subset with R1 resection (n=29), univariate analysis did not show that patients

without tumor fragmentation had a decreased risk for a second local relapse [HR 0.28 (CI95% 0.04-2.25); p=0.23]. For the subset with R0 resection (n=32), patients who did not receive EBRT experienced a significantly higher risk of local relapse in univariate analysis [HR 7.69 (CI95%1.0-56.9); p=0.05]. Alternatively, for the subset with R1 resection (n=16), univariate analysis did not show that patients not receiving EBRT had an increased risk for a second local relapse [HR 3.59 (CI95% 0.75-17.1); p=0.14]. When tumor fragmentation was evaluated in patients with and without EBRT to the pelvic LRR, we found that only for the subset with tumor fragmentation (n=21), not receiving EBRT showed worse LRC [HR 4.20 (CI95% 1.16-15.23); p=0.03]. For patients without tumor fragmentation (n=14) this analysis did not reach statistical significance [HR 3.22 (CI95% 0.51-9.23); p=0.25].

Causes of acute and chronic toxicity were estimated as multifactorial [17]. Overall 23 patients (38%) had grade ≥ 3 acute toxicity and 12 patients (20%) developed chronic toxicity ≥ 3 [Table 1]. Overall treatment mortality was 2.9% (n=1, wound infection-sepsis). No long-term treatment related death occurred. In relation to perioperative mortality no difference was found [3% (n=1) vs. 0% (n=0); p=0.65)] between patients treated for pelvic and paraaortic recurrence site.

Discussion

Our most relevant findings can be summarized as follows. First, we observed that not adding EBRT to surgery and IOERT to patients with ORGC was significantly associated with an increased probability of LRR, overall metastases and death [Figure 1D, E and F]. Interestingly, this association maintained significance in regard to LRR when patients with tumor fragmentation and R0 resection were analyzed separately. Second, patients with paraaortic LR had an increased risk of

overall metastases when compared to patients with pelvic LR. Third, we found that patients with a time interval < 24 months between primary tumor diagnosis and LR had an increased probability of LR and death. Finally, patients without tumor fragmentation had a decreased probability of LRR.

Oligometastasis implies a restricted locoregional tumor burden and has been proposed as a status candidate for intense treatment strategies combining surgery, radiotherapy and chemotherapy [1]. Oligotopic cancer has become synonymous with isolated metastases arising from micrometastases that have been dormant for variable periods of time [1]. Several IORT-expert institutions have analyzed mixed cohorts with broad inclusion criteria and reported results comparable to this retrospective single centre study [Supplementary Table 1]. The present analysis had no selection as to primary site, modalities of initial treatment, volume of tumor recurrence and included patients with pelvic and paraaortic ORGC. Discrimination between ORGC and primary advanced tumors is important because survival (10-year OS 14 vs. 67%; $p<0.001$) and local control (10-year IOERT in field control 47 vs. 93%; $p<0.001$) of patients treated for primary advanced disease has been reported to be superior [7].

Improved survival and LRC has been frequently reported to be associated to the achievement of a gross total resection (R0/R1 resection) prior to IORT [7, 13]. In an updated Mayo Clinic data [13] reported by Haddock et al. 148 patients (84% ORCG) with gynecological tumors were treated with maximal surgical resection plus IOERT (76% EBRT). The 5-year LRC and OS was 60% and 27% for the total group. Patients with an R2 resection had a significantly lower survival than patients with R0/R1 resection (5-year OS 13 vs. 31%; $p=0.01$). The distant metastases rate was decreased in patients with R0/R1 vs. R2 resection (5-year 49

vs. 58%), but LRC at 5-years was 74% for patients with R2 resection versus 58% for patients with R0/R1 resection. The high LRC in R2 patients may be explained to the increased rate of distant metastases and subsequent death before local relapse was clinically evident. Aubey et al. [18] reported 56 patients with ORGC that were treated with radical resection followed by high dose rate (HDR)-IORT. With a median follow-up of 11.4 months, 2-year survival rate for patients with R2 resections was 20% compared to 60% for those with R0/ R1 resections ($p<0.01$). A French multi-institutional analysis reported by Mahe et al. [9] observed no difference in the distant metastatic rate. However, because LRC rate in the R2 group was 16% it is likely that many of these patients died of uncontrolled local disease progression prior to distant metastases manifestation [9]. In the current series the use of an IOERT containing multimodality strategy has impacted the extent of surgical resection (no patient had gross residual disease); in regard to the extent of surgical resection (R0 vs. R1) we found no difference in LRC or OS. In the mentioned Mayo Clinic experience [13], a worse survival was reported for patients with a disease-free interval (DFI) ≤ 2-years compared to those with a DFI > 2-years (5-year OS 14 vs. 35%; $p=0.002$). Our observation that patients with a DFI < 24 months had worse overall outcomes than patients with a DFI ≥ 24 months is consistent with previously reported findings.

The clinical significance of including an EBRT-component in a multimodality IORT-containing treatment for ORGC is uncertain. Previously irradiated patients (with assumed radioresistant biology) have been associated to adverse and inferior results in reported, but this observation has not been confirmed in the current series or other expert institutional analysis [7, 13].

A combinatorial dose escalation strategy combining EBRT and IORT has not been

consistently associated with improved outcomes. The Mayo Clinic series of 25 recurrent endometrial cancer patients [12] showed that EBRT was associated with improved survival (p=0.019). In the Mayo Clinic series of 89 patients with cervical cancer [locally recurrent (83%) or primary advanced (17%)] treated with IOERT following surgical resection (69% received pre- or postoperative EBRT) [19]. Pelvic exenteration and perioperative EBRT were associated with improved LRC on multivariate analysis. Consistently, with this finding we found that patients without EBRT treatment of the LR had inferior overall outcomes than patients treated with EBRT. Even more, patients with tumor fragmentation and R0 resection treated without EBRT had worse LRC than those who did received EBRT treatment. However, the optimal treatment sequence together with the contribution of an external beam radiation therapy (EBRT) component in this clinical scenario remains to be elucidated.

It has been reported that patients with ORGC exclusively in the paraaortic region can achieve excellent LRC and survival with salvage therapy [20]. In the current analysis, although paraaortic isolated lymph node recurrence was associated with equivalent LRC and survival rates when compared to pelvic recurrence, an increased incidence of overall metastases was observed suggesting a superior migration potential.

The interpretation of treatment related toxicity, tolerance and rate of postsurgical complications suggests that a multimodality approach including an IORT component for ORGC is feasible with tolerable risks and not limited by prohibitive long-term side effects.

We acknowledge several limitations of our study. First, the population was heterogeneous, having been treated over 18-years and receiving different

treatment combinations. Although we did observe an association between EBRT treatment and LRC after adjustment for several potential confounding factors, the presence of a selection bias for patients referred for radiation therapy to a higher dose cannot be completely dismissed. We certainly acknowledge that patients that did not consent EBRT had greater concerns related to re-treatment toxicity or issues related to treatment efficacy. A systematic method of follow-up, including imaging, would be optimal to evaluate patterns of failure after radiation therapy [21, 22]. Given the retrospective nature of this analysis, consistent homogeneous imaging did not occur in a proportion of patients. Therefore, a significant number of patients with distant only recurrence may not have undergone optimal imaging of the pelvis at the time of recurrence. Finally, it must be emphasized that systemic therapy plays an important role in the management of ORGC (specially in patients with paraaortic lymph node metastases).

In conclusion, we found that ORGC patients that received EBRT and IOERT were treated safely and had improved rates of LRC. We also found that patients with tumor fragmentation and R0 resections experienced the largest benefit with EBRT treatment. A certain level of prognostic adversity (non-radical resections) might be compensated by the addition of EBRT. Our results suggest that a subgroup of patients with ORGC could benefit from intensive local treatment to the isolated local relapse.

Figure 1. Kaplan-Meier curves of all patients (n=61) for overall survival (A), disease-free survival (B) and local-regional control (C). Overall survival (D), disease-free survival (E) and local-regional control (F) according to EBRT treatment to the local relapse or not.

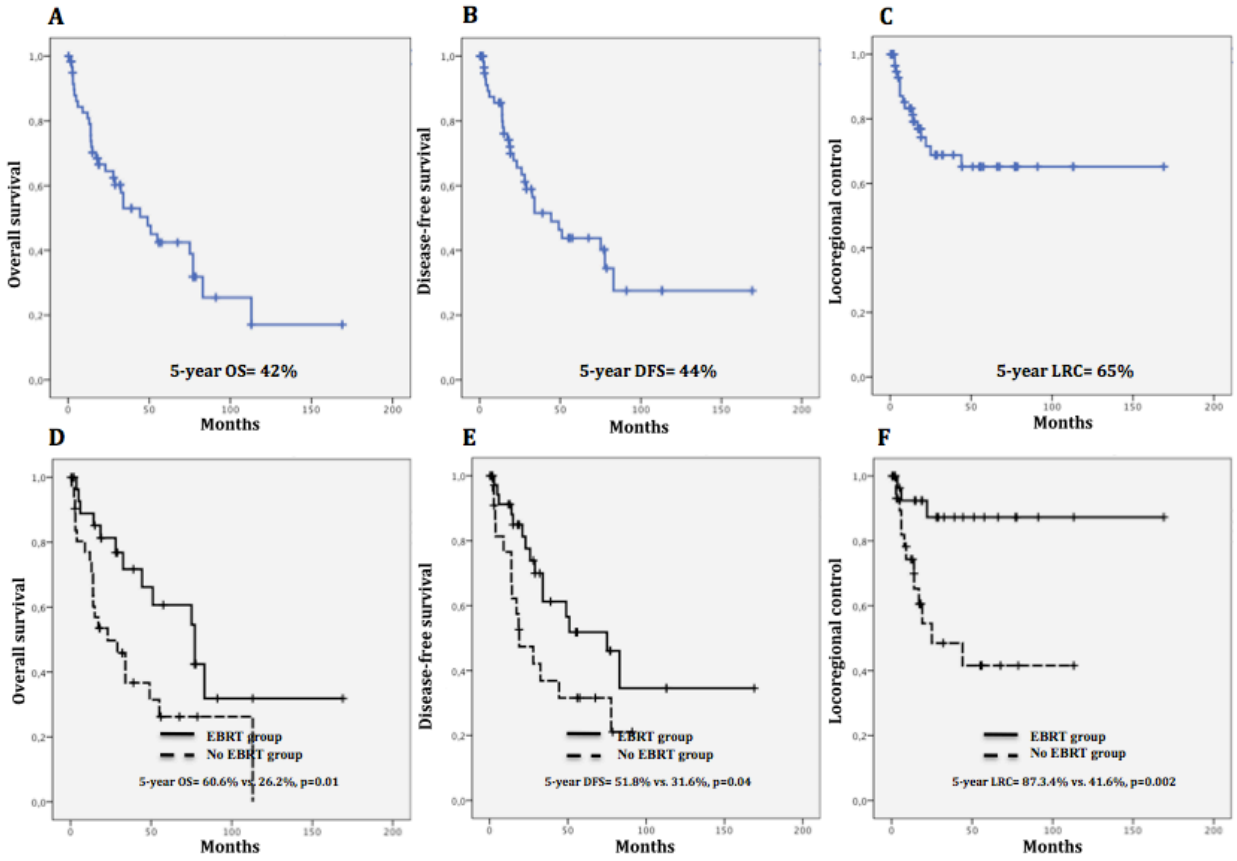


Table 1. Patient, tumor and treatment characteristics

Characteristics	All patients N=61 (%)	Pelvic N=35 (%)	Paraaortic N=26 (%)	P-value
PATIENT VARIABLES				
Median age (range)	55 (38-67)	53 (38-67)	57 (40-65)	0.18
Karnofsky performance status ≥ 90/ < 90	34 (56)/ 27 (44)	24 (69)/ 11 (31)	10 (38)/ 16 (62)	0.15
Time interval (months) from primary to LR (range) ≥ 24 / < 24	35 (57)/ 26 (43)	19 (54)/ 16 (46)	16 (62)/ 10 (38)	0.28
MACROSCOPIC TUMOR VARIABLES				
Primary site Endometrial/ uterine cervix/ ovarian/ vagina	18 (30)/ 32 (52)/ 9 (15)/ 2 (3)	7 (20)/ 20 (57)/ 6 (17)/ 2 (6)	11 (42)/ 12 (46)/ 3 (12)/ 0	0.14
Maximum recurrent tumor diameter ≥ 5 cm vs < 5 cm	34 (56)/ 27 (44)	17 (45)/ 18 (55)	17 (65)/ 9 (35)	0.14
Tumor multifragmentation involvement Yes vs No	38 (62)/ 23 (38)	21 (60)/ 14 (40)	17 (65)/ 9 (35)	0.78
MICROSCOPIC TUMOR VARIABLES				
Initial primary tumor histological grade I-II vs III	43 (70)/ 18 (30)	26 (74)/ 9 (26)	17 (65)/ 9 (35)	0.41
Histologic subtype Adenocarcinoma/ squamous carcinoma	35 (57)/ 26 (43)	20 (57)/ 15 (43)	15 (58)/ 11 (42)	0.95
Margin status R0 vs R1	32 (52)/ 29 (48)	19 (54)/ 16 (46)	13 (50)/ 13 (50)	0.74
Surgical variables				
Bone resection Yes vs No	11 (18)/ 50 (82)	6 (17)/ 29 (83)	5 (19)/ 21 (81)	0.86
Vascular resection Yes vs No	7 (11)/ 54 (89)	5 (14)/ 30 (86)	2 (8)/ 24 (91)	0.56
Soft tissue resection Yes vs No	35 (57)/ 26 (43)	20 (57)/ 15 (43)	15 (58)/ 11 (42)	0.95
RADIATION THERAPY AND CHEMOTHERAPY VARIABLES				
Surgical resection treatment for initial primary tumor Yes vs No	44 (72)/ 17 (28)	26 (74)/ 9 (26)	18 (69)/ 8 (31)	0.63
Adjuvant chemotherapy initial primary tumor Yes vs No	33 (54)/ 28 (46)	21 (60)/ 14 (40)	12 (46)/ 14 (54)	0.28
EBRT for initial primary tumor Yes vs No	40 (66)/ 21 (34)	25 (71)/ 10 (29)	16 (62)/ 10 (38)	0.25
Adjuvant chemotherapy for recurrent tumor Yes vs No	24 (39)/ 37 (61)	13 (37)/ 22 (63)	11 (42)/ 15 (58)	0.57
EBRT for recurrent tumor Yes vs No	29 (48)/ 32 (52)	16 (46)/ 19 (54)	13 (50)/ 13 (50)	0.74
IOERT dose ≥ 12.5 Gy vs < 12.5 Gy	41 (67)/ 20 (33)	22 (63)/ 13 (37)	19 (73)/ 7 (23)	0.38
HOSPITALIZATION				
Median time (minutes) of surgery	428 (188-950)	452 (205-950)	409 (188-625)	0.31
Median time (days) admitted to the intensive care unit	2.5 (0-9)	2.5 (0-9)	2.3 (0-7)	0.41
Median time (days) of overall hospitalization	20 (4-138)	20 (4-138)	18 (4-56)	0.31
TOXICITY				
RTOG Chronic toxicity ≥ 3 ***Gastrointestinal (Fistula n=5; abscess n=3)*** ***Genitourinary (Ureteral stenosis n=3)*** ***Nervous (Peripheral neuropathy n=1)***	12 (20)	8 (23)	4 (15)	0.22
Clavien-Dindo perioperative complications	34 (56)	20 (57)	14 (54)	0.62

RTOG Acute toxicity ≥ 3 ***Gastrointestinal (n=3)*** ***Genitourinary (n=5)*** ***Soft tissue (n=1)*** ***Wound infection (n=3)*** ***Cardiac (n=1)*** ***Pulmonary (n=1)***	23 (38)	14 (40)	9 (35)	0.79

EBRT, external beam radiation therapy. RTOG, radiation therapy oncology group

Table 2. Correlations between macroscopic/microscopic pathology characteristics and IOERT technical parameters

Pathology/ IOERT Treatment	**Surgical specimens**	**Applicator size**	**IOERT dose (Gy)**	**IORT energy (MeV)**
		Median/ range	**Median/ range**	**Median/ range**
Total number of involved fragments				
1	28	8/ 5-12	12.5/ 10-15	10/ 6-15
2	10	9/ 5-12	12.5/ 10-15	9/ 6-18
3	13	8/5-12	12.5/ 10-15	12/ 9-18
4-6	10	8/5-10	12.5/10-15	12/6-18
Tmax size (cm)				
1.0-2.0	8	5/ 5-12	12.5/ 12.5-15	12/ 6-18
2.1-4.0	19	8/ 5-10	12.5/ 10-15	12/ 6-18
4.1-7.0	19	8/ 5-10	12.5/ 10-15	12/ 6-15
7.1-11.0	15	10/ 7-12	12.5/ 10-12.5	10/ 6-15

Tmax= tumoral maximal dimension

Table 3. Univariate analyses of associations between the patient, tumor, treatment, and pathologic characteristics and survival

Parameter	Variable	Locoregional control			Disease free survival			Overall survival		
		HR	CI 95%	P value	HR	CI 95%	P value	HR	CI 95%	P value
PATIENTS										
Age (years)	***≤ 55*** ***> 55***	1.0 0.58	0.22-1.57	0.28	1.0 0.78	0.38-1.59	0.49	1.0 0.94	0.48-1.87	0.87
Karnofsky performance status	***> 90*** ***≤ 90***	1.0 1.52	0.55-4.20	0.42	1.0 1.63	0.75-3.53	0.22	1.0 1.77	0.84-3.70	0.13
Time interval from primary tumor to LR	***≥ 24 months*** ***< 24 months***	1.0 3.23	1.12-9.09	**0.03**	1.0 4.97	1.32-8.33	**0.01**	1.0 4.17	1.27-7.69	**0.01**
MACROSCOPIC SURGICAL SPECIMEN										
Primary site	***Endometrial*** ***Uterine cervix*** ***Ovarian***	1.0 1.64 0.75	 0.51-5.26 0.14-4.16	 0.41 0.75	1.0 3.98 2.83	 0.43-32.81 0.36-22.19	 0.22 0.32	1.0 1.35 0.55	 0.64-2.86 0.19-1.57	 0.43 0.26
Recurrence site	***Pelvic*** ***Paraaortic***	1.0 0.60	0.20-1.88	0.38	1.0 2.07	1.0-4.25	**0.05**	1.0 1.52	0.76-3.05	0.23
Recurrent tumor Tumor size	***> 5*** ***≤ 5***	1.0 1.28	0.41-3.97	0.67	1.0 1.78	0.68-4.66	0.24	1.0 1.79	0.74-4.34	0.22
Tumor multifragmentation involvement	***Yes*** ***No***	1.0 0.16	0.04-0.71	**0.02**	1.0 0.67	0.21-1.34	0.15	1.0 0.63	0.31-1.27	0.20
MICROSCOPIC SURGICAL SPECIMEN										
Primary tumor histologic grade	***I-II*** ***III***	1.0 1.73	0.64-4.67	0.28	1.0 2.37	1.15-4.88	**0.02**	1.0 1.78	1.18-4.87	0.10
Histologic subtype	***Adenocarcinoma*** ***Squamous cell***	1.0 3.11	1.13-8.57	**0.03**	1.0 1.56	0.74-3.32	0.25	1.0 1.52	0.72-3.17	0.23
Recurrent tumor Margin status	***R0*** ***R1***	1.0 2.09	0.76-5.76	0.15	1.0 1.37	0.68-2.88	0.36	1.0 1.33	0.68-2.16	0.41
Recurrent tumor Lymph node	***Positive*** ***Negative***	1.0 0.76	0.26-2.20	0.62	1.0 1.45	0.62-3.09	0.32	1.0 1.52	0.77-3.0	0.23
SURGERY										
Multiorgan resection	***Yes*** ***No***	1.0 0.80	0.30-2.15	0.66	1.0 0.56	0.25-1.26	0.16	1.0 0.76	0.37-1.56	0.45
Vascular resection	***Yes*** ***No***	1.0 0.28	0.06-1.26	0.10	1.0 0.56	0.13-2.38	0.43	1.0 0.64	0.15-2.69	0.54
Bone resection	***Yes*** ***No***	1.0 0.27	0.04-2.0	0.20	1.0 0.66	0.23-1.90	0.44	1.0 0.62	0.22-1.79	0.38
Soft tissue resection	***Yes*** ***No***	1.0 0.38	0.12-1.17	0.09	1.0 0.95	0.46-1.97	0.90	1.0 0.93	0.47-1.83	0.83
TREATMENT										
Primary tumor surgical treatment	***Yes*** ***No***	1.0 2.89	0.66-8.73	0.26	1.0 1.30	0.56-3.03	0.55	1.0 2.34	0.71-7.15	0.20
Primary tumor RT treatment	***Yes*** ***No***	1.0 0.96	0.34-2.82	0.96	1.0 1.80	0.85-3.79	0.13	1.0 1.73	0.85-3.56	0.13
Primary tumor Adjuvant CT	***Yes*** ***No***	1.0 0.74	0.28-1.98	0.55	1.0 0.80	0.39-1.64	0.54	1.0 0.75	0.38-1.48	0.40
Recurrent tumor RT treatment	***Yes*** ***No***	1.0 5.73	1.62-20.24	**0.007**	1.0 1.90	1.01-3.99	**0.05**	1.0 2.39	1.18-4.87	**0.02**
Recurrent tumor Adjuvant CT	***Yes*** ***No***	1.0 0.81	0.26-2.56	0.72	1.0 0.60	0.22-1.67	0.32	1.0 0.76	0.31-1.86	0.54
IOERT dose	**≥ 12.5 Gy** **< 12.5 Gy**	1.0 2.15	0.69-6.68	0.18	1.0 1.77	0.78-4.45	0.18	1.0 1.87	0.78-5.20	0.21
IOERT fields	**1** **2**	1.0 2.04	0.58-7,18	0.27	1.0 1.16	0.52-2.57	0.72	1.0 1.22	0.55-2.74	0.62

Table 4. Factors associated with locoregional control, distant metastases-free survival, disease-free survival and overall survival in multivariate analyses

Parameter	**Variable**	**Locoregional control**			**Disease free survival**			**Overall survival**		
		HR	CI 95%	P value	HR	CI 95%	P value	HR	CI 95%	P value
Recurrence site	***Pelvic*** ***Paraaortic***	-	-	-	1.0 2.27	1.10-4.38	**0.04**	-	-	-
Time interval from primary tumor to LR	***≥ 24 months*** ***< 24 months***	1.0 4.02	1.20-14.29	**0.02**	-	-	-	1.0 2.32	1.16-4.76	**0.02**
Tumor fragmentation	***Yes*** ***No***	1.0 0.22	0.17-0.88	**0.03**	-	-	-	-	-	**-**
Recurrent tumor RT treatment	***Yes*** ***No***	1.0 3.95	1.21-10.92	**0.02**	1.0 3.52	1.11-6.32	**0.04**	1.0 3.77	1.08-8.87	**0.04**

References.

[1]. Weichselbaum RR, Hellman S. Oligometastases revisited. Nat Rev Clin Oncol. 201; 8: 378-82.

[2]. Hockel M, Dornhofer N. Pelvic exenteration for gynaecological tumours: Achievements and unanswered questions. Lancet Oncol. 2006; 7: 837–847.

[3]. Perez CA, Kuske RR, Camel HM, et al. Analysis of pelvic tumor control and impact on survival in carcinoma of the uterine cervix treated with radiation therapy alone. Int J Radiat Oncol Biol Phys. 1988; 14: 613–621.

[4]. Garton GR, Gunderson LL, Webb MJ, et al. Intraoperative radiation therapy in gynecologic cancer: Update of the experience at a single institution. Int J Radiat Oncol Biol Phys. 1997; 37: 839–843.

[5]. Gemignani ML, Alektiar KM, Leitao M, et al. Radical surgical resection and high-dose intraoperative radiation therapy (HDRIORT) in patients with recurrent gynecologic cancers. Int J Radiat Oncol Biol Phys. 2001; 50: 687–694.

[6]. Stelzer KJ, Koh WJ, Greer BE, et al. The use of intraoperative radiation therapy in radical salvage for recurrent cervical cancer: Outcome and toxicity. Am J Obstet Gynecol. 1995; 172: 1881–1888.

[7]. Martínez-Monge R, Jurado M, Aristu JJ et al. Intraoperative electron beam radiotherapy during radical surgery for locally advanced and recurrent cervical cancer. Gynecol Oncol. 2001; 82: 538-43.

[8]. del Carmen MG, Eisner B, Willet CG, et al. Intraoperative radiation therapy in the management of gynecologic and genitourinary malignancies. Surg Oncol Clin North Am. 2003; 12: 1031–1042.

[9]. Mahe MA, Gerard JP, Dubois JB, et al. Intraoperative radiation therapy in recurrent carcinoma of the uterine cervix: Report of the French intraoperative

group on 70 patients. Int J Radiat Oncol Biol Phys. 1996; 34: 21–26.

[10]. Tran PT, Su Z, Hara W, et al. Long-term survivors using intraoperative radiotherapy for recurrent gynecologic malignancies. Int J Radiat Oncol Biol Phys. 2007; 69: 504-11.

[11]. Barney BM, Petersen IA, Dowdy SC, et al. Long-term outcomes with intraoperative radiotherapy as a component of treatment for locally advanced or recurrent uterine sarcoma. Int J Radiat Oncol Biol Phys. 2012; 83: 191-7.

[12]. Dowdy SC, Mariani A, Cliby WA, et al. Radical pelvic resection and intraoperative radiation therapy for recurrent endometrial cancer: Technique and analysis of outcomes. Gynecol Oncol. 2006; 101: 280–286.

[13]. Haddock MG, Martinez-Monge R, Petersen IA, Wilson TO. Locally advanced primary and recurrent gynecological malignancies: EBRT with or without IOERT or HDR-IORT. In: Gunderson LL, Willett CG, Calvo FA, et al. editors. Intraoperative irradiation. Techniques and results. 2nd ed. Springer New York: Humana Press; 2011.

[14]. Pascau J, Santos Miranda JA, Calvo FA, et al. An innovative tool for intraoperative electron beam radiotherapy simulation and planning: description and initial evaluation by radiation oncologists. Int J Radiat Oncol Biol Phys. 2012; 83: 287-295.

[15]. Clavien PA, Barkun J, de Oliveira ML, et al. The Clavien-Dindo classification of surgical complications: five-year experience. Ann Surg. 2009; 250: 187-96.

[16]. Cox JD, Stetz J, Pajak TF. Toxicity criteria of the Radiation Oncology Group (RTOG) and the European Organization for Research and Treatment of Cancer (EORTC). Int J Radiat Oncol Biol Phys. 1995; 31: 1341–1346.

[17]. Azinovic I, Calvo FA, Puebla F, et al. Long-term normal tissue effects of

intraoperative electron radiation therapy (IOERT): late sequelae, tumor recurrence, and second malignancies. Int J Radiat Oncol Biol Phys. 2001; 49: 597–604.

[18]. Aubey JJ, McCreath W, Chi DS, et al. Outcomes of patients with recurrent gynecological malignancues treated with with radical surgical resection and high-dose rate intraoperative radiotherapy (HDR-IORT). The 35th Annual SGO meeting in San Diego, CA; 2004.

[19]. Barney BM, Petersen IA, Dowdy SC. et al. Intraoperative Electron Beam Radiation Therapy (IOERT) in the Management of Locally Advanced or Recurrent Cervical Cancer. Radiat Oncol. 2013; 8: 80. [Epub ahead of print]

[20]. Singh AK, Grigsby PW, Rader JS, et al. Cervix carcinoma, concurrent chemoradiotherapy, and salvage of isolated paraaortic lymph node recurrence. Int J Radiat Oncol Biol Phys. 2005; 61: 450-5.

[21]. Brocker KA, Alt CD, Eichbaum M, et al. Imaging of female pelvic malignancies regarding MRI, CT, and PET/CT : part 1. Strahlenther Onkol. 2011; 187: 611-8.

[22]. Alt CD, Brocker KA, Eichbaum M, et al. Imaging of female pelvic malignancies regarding MRI, CT, and PET/CT: Part 2. Strahlenther Onkol. 2011; 187: 705-14.

Prognostic Value of External-Beam Radiation Therapy in Patients treated with Surgical Resection and Intraoperative Electron-Beam Radiation Therapy for Locally Recurrent Soft Tissue Sarcoma: A multicentric long-term outcome analysis

Felipe A. Calvo, M.D., Ph.D., [1,2] Claudio V. Sole, M.D., [1-3] Mauricio Cambeiro, M.D., Ph.D., [4] Angel Montero, M.D., [5] Alfredo Polo, M.D., Ph.D., [5] Carmen Gonzalez, M.D., [2-6] Miguel Cuervo, M.D., [7] Mikel San Julian M.D., [9] Jose L. Garcia-Sabrido M.D., Ph.D., [2, 10] Rafael Martinez-Monge, M.D., Ph.D., [4]

[1] Department of Oncology. Hospital General Universitario Gregorio Marañón. Madrid, Spain.

[2] School of medicine. Complutense University. Madrid, Spain.

[3] Service of Radiation Oncology. Instituto de Radiomedicina. Santiago, Chile.

[4] Service of Radiation Oncology. Clínica Universitaria. Universidad de Navarra. Pamplona, Spain.

[5] Service of Radiation Oncology. Hospital Universitario Ramón y Cajal. Universidad de Alcala. Madrid, Spain.

[6] Service of Radiation Oncology. Hospital General Universitario Gregorio Marañón. Madrid, Spain.

[7] Service of Orthopedics and Traumatology. Hospital General Universitario Gregorio Marañón. Madrid, Spain.

[8] Service of Orthopaedics and Traumatology. Hospital Universitario Ramón y Cajal. Universidad de Alcala. Madrid, Spain.

[9] Service of Orthopedics and Traumatology. Clínica Universitaria. Universidad de Navarra. Pamplona, Spain.

[10] Service of General Surgery III. Hospital General Universitario Gregorio Marañón. Madrid, Spain.

Running title: [IORT for locally recurrent soft tissue sarcoma]

Corresponding author: Claudio V. Sole, M.D.
Hospital General Universitario Gregorio Marañon, Madrid, Spain.
C/ Doctor Esquerdo, 46 - 28007 Madrid.
Phone:+ (34) 91 586 85 99. Fax:+ (34) 91 426 93 89. Email: cvsole@uc.cl

Abstract

Background: A joint analysis of data from centers involved in the Spanish Cooperative Initiative for Intraoperative Electron Radiotherapy (IOERT) was performed to investigate long-term outcomes of locally recurrent soft tissue sarcoma (LR-STS) patients treated with a multidisciplinary approach.

Methods: Patients with a histological diagnosis of LR-STS (extremity, 43%; trunk wall, 24%; retroperitoneum, 33%) and no distant metastases who underwent radical surgery and IOERT (median dose, 12.5 Gy) were considered eligible for participation in this study. Additionally, 62% received external beam radiotherapy (EBRT: median dose, 50 Gy).

Results: From 1986 to 2012, a total of 103 patients from 3 Spanish expert IOERT institutions were analyzed. With a median follow-up of 57 months (range, 2-311), 5-year local control (LC) was 60%. Five-year IORT in-field control, disease-free survival (DFS), and overall survival were 73%, 43%, and 52%, respectively. In the multivariate analysis, no EBRT to treat the LR-STS (p=0.02) and microscopically involved margin resection status (p=0.04) retained significance in relation to LC. With regard to IORT in-field control, only not delivering EBRT to the LR-STS retained significance in the multivariate analysis (p=0.03).

Conclusion: This joint analysis revealed that surgical margin and EBRT affect LC, but given the high risk of distant metastases, DFS remains modest. Intensified local treatment needs to be further tested in the context of more efficient concurrent, neoadjuvant, and adjuvant systemic therapy.

Keywords: intraoperative radiotherapy; external-beam radiotherapy; soft-tissue sarcoma; local recurrence; long-term outcomes

Introduction

Soft tissue sarcomas (STS) are uncommon tumors with heterogeneous biological properties and histological findings [1]. Complete resection is the primary therapy for most STS in adults, but patients with locally recurrent STS (LR-STS) have poor local control and survival [2]. Clinical practice has shifted from non-intervention or palliative treatment to more intensive multimodal approaches with radical rescue surgery providing local control in approximately half of all patients [3-4]. The success of rescue treatment is highly dependent on the extent of local extension, invasion, fixation, and radicality of resection [2-4]. A completely negative resection margin is often difficult to achieve owing to close proximity to or proven invasion of adjacent post-resection tumor bed areas, or unresectable structures. Therefore, multimodal approaches including additional local therapies should be implemented to further improve patient outcomes and optimize local control and survival [5]. Few studies have specifically analyzed the prognosis of patients with LR-STS involving the extremities, trunk wall, and retroperitoneum [6-13]. We performed a joint study of data from the Spanish Cooperative Initiative for Intraoperative Electron-beam Radiotherapy (IOERT) to analyze long-term outcomes and novel risk factors for a group of patients with LR-STS treated with radical surgery and IOERT in high-risk areas (postresection and pre-reconstruction) with and without external beam radiation therapy (EBRT).

Materials and Methods

Patient characteristics and staging evaluation

This study was approved by our institutional review board and performed in compliance with local ethical and clinical practice guidelines. The study population

comprised adult patients (>18 years) with pathologically confirmed nonmetastatic LR-STS and curative resections with either close (<1 cm) or positive margins. The tumor board recommended a multimodal approach after taking into account initial treatment characteristics, location, resectability, and clinical status. All (n=103) patients were offered to participate in a developmental protocol that consisted of rescue surgery, EBRT and IOERT delivered to the area of the tumor bed that was at risk for residual disease EBRT plus IOERT program, but 40 (39%) elected not to consent the EBRT component (patients that did not consent EBRT had greater concerns related to re-treatment toxicity or issues related to treatment efficacy). Two treatment strategies were operational along the period: 63 (61%) patients were treated according to a research protocol that consisted of EBRT, surgery and IOERT with or without adjuvant chemotherapy (EBRT group). The remaining 40 patients were treated with surgery plus IOERT, but without EBRT (non-EBRT group) and served as the control cohort. The surgical approach and adjuvant chemotherapy were discussed on an individual basis. Prospectively collected hospital records of 103 patients registered in the IOERT program and treated for LR-STS between June 1986 and April 2012 were retrospectively reviewed at the time of scheduled follow-up. Pretreatment evaluation consisted of a complete history and physical examination, complete blood count, renal and liver function tests, chest X-ray, and computerized tomography (CT) or magnetic resonance imaging (MRI) of the tumor site, chest, and abdomen. Patients were reclassified according to the 7th AJCC/UICC staging system. Patient and treatment characteristics are listed in Table 1. No significant differences in baseline variables were detected between patients treated with or without EBRT.

Treatment characteristics

EBRT and concomitant and adjuvant chemotherapy were administered following standards described elsewhere [5]. Conformal 3-dimensional postoperative EBRT (n=63, 62%) was delivered with megavoltage equipment (6 to 15 MV). Fields were arranged taking into account doses delivered to normal tissues during radiotherapy for the primary tumor. However, no specific dose-volume constraints were indicated in the treatment protocol. Non-irradiated patients (n=46) received a total median dose of 50 Gy (range, 45 to 50.4 Gy [1.8-2.0 Gy/5 d/wk]) and re-irradiated patients (n=17) received 30.6 Gy (range, 21.6 to 30.6 Gy [1.8 Gy/5 d/wk]), both of which were prescribed to the isodose line that covered the planning target volume (PTV) to obtain a homogeneity of **±** 5% of the prescribed dose according to the International Commission on Radiation Units and Measurements Report No. 50. The technique for the EBRT component consisted in conventional (2D-RT) EBRT for patients treated between 1986 and 1992 (n=12, 20%), and conformal (3D-CRT) EBRT for patients treated after 1992 (n=49, 80%). PTV for 2D-RT was defined as tumour bed plus 3 cm in the radial directions in all cases, and for the longitudinal directions a 5 cm margin was applied for extremity LR-STS and a 3 cm margin was added for trunk wall and retroperitoneal LR-STS (the field could be shortened to include the end of the compartment). Clinical target volume (CTV) for 3D-CRT technique included the surgical tumor bed plus a 2 cm margin in the radial directions. A 3 cm margin in the longitudinal (proximal and distal) directions was used in the case of extremity locations, and for trunk wall and retroperitoneal LR-STS, a 2 cm margin was used. PTV was defined as CTV plus a 1 cm margin in longitudinal and radial directions. The surgical approach (4-6 weeks before EBRT treatment) consisted of wide resection (62%) or marginal resection (38%). Patients with a higher histological grade (grade 3) and tumor size

(≥5 cm) were offered adjuvant chemotherapy (most commonly 4 or 5 cycles of doxorubicin 75 mg/m^2 and ifosfamide 5 g/m^2 every 3 weeks). The IOERT program was performed in a non-dedicated linear accelerator under an outpatient regimen. After resection and before reconstruction, 10 to 20 Gy (median, 12.5 Gy) were delivered in a single fraction to 1-field PTVs (n=75, 73%) or 2-field PTVs (n=28, 27%) using a median energy of 9 MeV (range, 4 to 20 MeV) (Table 2). The dose was delivered to the 90% isodose line covering the surgical bed. The IOERT dose was chosen according to the EBRT dose, margins (intraoperative margin status was assessed using frozen pathologic sections) and surgical bed volumes. Beveled (15-45º) Lucite circular applicators (size range, 5 to 15 cm) were adjusted to collimate the target surface air gap, thus allowing dosimetric adaptation and uniform dose distribution. IOERT CT-guided treatment has been available since 2008 [14].

Follow-up and toxicity evaluation

All patients were followed according to a common protocol every 3 months after completion of treatment for the first 3 years and every 6 months for an additional 3 years thereafter. Patients were restaged 4 weeks after EBRT and routinely every 6 months with chest X-ray and computed tomography or magnetic resonance imaging of the initial tumor site.

Acute and late toxicities were evaluated according to the criteria of the Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer [15].

Statistical analysis

Data were analyzed using SPSS (version 19.0). The primary endpoint of the analysis was local control (freedom from EBRT in-field progression). Secondary

endpoints were IOERT in-field control (freedom from IOERT in-field progression), disease-free survival (DFS), and overall survival (OS). Potential associations for survival outcomes were assessed in the univariate and multivariate analyses using the Cox proportional hazards model. Based on p values ≤0.10 in the univariate analysis and clinical relevance, multivariate analysis was performed using a stepwise regression model to identify variables that have an effect on survival outcomes ($p \leq 0.05$, 2-sided).

Results

Median follow-up time for all patients was 57 months (range, 2-311). Forty-one patients remained alive at the time of the analysis. Median follow-up for surviving patients was 80 months (range, 4-311). Of the 62 deceased patients, 55 (89%) died from progression of sarcoma, and 7 (11%) died from causes unrelated to their sarcomas or treatment. The crude local relapse rate was 34% (n=35); 36% (n=37) developed distant metastases (most commonly pulmonary [n=18, 49%]). Of the 35 patients who had local progression, 18 (51%, crude rate) underwent a new surgical procedure for rescue [median time to surgical rescue 23.3 months (range, 6.7-61.4)], with long-term local sarcoma control in 11 (61%, crude rate). The remaining 17 patients had synchronous distant metastases with local relapse and received chemotherapy alone (n=82%) or no further therapy (n=18%).

Local control for the study population at 5 and 10 years was 60% and 58% (Figure 1A). Univariate Cox proportional hazard analyses showed that patients with a time interval from primary tumor diagnosis to local relapse <24 months (p=0.04), incomplete resection (p=0.02), high histological grade (p=0.05), and no EBRT administered to treat the LR-STS (p=0.04) were associated with a higher

probability of local relapse (Table 3). After adjustment for other covariates, the variables that remained significantly associated with local relapse were no EBRT to the LR-STS (p=0.02) and R1 margin status (p=0.04) (Table 4). IOERT in-field control at 5 and 10 years was 73% and 70% (Figure 1B). Univariate analysis showed that patients with R1 resection (p=0.05) and no EBRT to treat the LR-STS (p=0.05) had a higher probability of IOERT in-field relapse (Table 3). In the multivariate analysis, only no EBRT to treat the LR-STS (p=0.03) retained a significant association with regard to IOERT in-field relapse (Table 4). DFS at 5 and 10 years was 43% and 33% (Figure 1C). Univariate Cox proportional hazard analysis showed that time interval from primary tumor diagnosis to local relapse <24 months (p=0.01), high histological grade (p=0.02), and R1 resection status (p=0.04) were associated with a higher probability of metastasis (Table 3). After adjustment for other covariates, primary tumor diagnosis to local relapse <24 months (p=0.006), high histological grade (p=0.04), and incomplete margin status (p=0.03) retained a significant association with DFS (Table 4). Overall survival at 5 and 10 years was 52% and 33% (Figure 1D). In the univariate analysis, patients with age ≥50 years (p=0.05), a time interval from primary tumor diagnosis to local relapse <24 months (p=0.01), and an R1 margin status (p=0.04) were at a significantly higher risk of death (Table 3). Multivariate analysis showed that only R1 margin status (p=0.02) and primary tumor diagnosis to local relapse <24 months (p=0.006) were significantly associated with OS (Table 4).

Overall, 16 patients (16%) had grade ≥ 3 acute toxicity (severe skin reactions [n=7, grade 3] and wound-healing disorders [n=5, grade 3; n=4, grade 4]). Severe skin reactions and wound-healing disorders were more frequently observed in patients with extremity LR-STS (n=3, grade 3) and trunk wall LR-STS [n=2, grade

3; n=2, grade 4]), respectively. Thirteen patients (13%) developed chronic toxicity ≥3 (neuropathy [n=6, grade 3], necrosis/fistula/ulcer [n=3, grade 3], and severe chronic lymphedema [n=7, grade 3]). Neuropathy, necrosis/fistula/ulcer and severe chronic lymphedema were more frequently observed in patients with retroperitoneal LR-STS (n=3, grade 3), trunk wall LR-STS (n=2, grade 3) and extremity LR-STS (n=7, grade 3), respectively. No significant differences were observed in acute or chronic toxicity between patients who received EBRT to treat the local relapse and those who did not. No perioperative deaths or deaths related to long-term treatment were recorded.

Discussion

To our knowledge, this is the first study to focus on long-term outcomes in patients with LR-STS treated with IOERT, surgical resection and EBRT. Our most relevant findings can be summarized as follows. First, we observed that not combining EBRT with surgical resection and IOERT in patients with LR-STS was significantly associated with an increased probability of LR and IOERT in-field relapse. Second, we found that patients with a time interval <24 months between primary tumor diagnosis and local relapse had an increased probability of overall metastasis and death. Finally, patients with microscopically positive margins had worse overall outcomes.

Several expert IOERT institutions with broad inclusion criteria (primary advanced and locally recurrent) and mixed cohorts of extremity, trunk wall, and retroperitoneal sarcomas have reported results comparable to those of the present analysis [Table 5]. The present retrospective single-center analysis included only patients with LR-STS. Selection was not based on primary site, volume of tumor

recurrence, or modalities of initial treatment. All cases had close margins (<1 cm) or positive margins (R1), features related to difficult surgical resection and adverse prognosis [3].

Discrimination between primary advanced and LR-STS in IOERT-based studies is important, because worse overall outcomes are consistently described for LR-STS [5, 6]. Several groups have successfully implemented and reported combined management (IORT and surgical resection) in mixed cohorts for patients with primary and LR-STS (5-year local control [60-80%]) [11-13].

Although it is widely accepted that the quality of the surgical margin is of paramount importance for local control, what constitutes adequate surgical margins is not well established. Positive surgical margins have been consistently reported as an adverse prognostic factor for local control [12, 13]. Oertel et al. [12] reported high 5-year local control (78%) and OS (77%) in the largest single institution experience reported to date (n=153), in which IOERT combined with moderate doses of EBRT for the management of extremity STS (32% recurrent). Local control was more favorable for patients with complete margin resection (5-year locoregional control 85% vs 60%, p=0.03). Azinovic et al. [13] analyzed 45 patients with extremity sarcomas (42% recurrent tumors) treated with moderate-dose postoperative EBRT (45 to 50 Gy) and IOERT. Five-year local control was 87%, and margin status (negative or close margins vs. positive margins [p=0.04]) significantly affected local control. In the current analysis, positive microscopic resection margins were significantly associated with poor overall outcomes in the multivariate analysis. Nonetheless, in order to compare results from different institutional experiences and to evaluate the effect of different treatment modalities on local control, a strict definition of the margin assessment procedure

is required. Several routines for margin assessment have been described [16]. Most studies report that the margin is assessed by the surgeon and validated by the pathologist or jointly assessed by the two. The surgeon can measure the thickness of the closest margin of surrounding tissue on the fresh specimen, omitting areas of shortest distances where there is fascial involvement. The pathologist can measure the thickness of the tumor macroscopically on fresh or formalin-fixed specimen using several slices. In recent years, reports on the surgical margin have generally been accompanied by the microscopic tumor tissue location at the specimen perimeter [17]. Finally, the shortest distance without fascial coverage can be measured microscopically as the distance from tumor tissue to an inked surface [16]. Interpretation of these anatomical and histological features is even more uncertain in post-resection and irradiated sarcoma specimens. In the present analysis, the pathologist defined a positive margin during surgery using frozen section analysis.

Histological grade is an independent predictive factor for development of metastasis in most cases of adult STS [4]. Unsurprisingly, therefore, grade was also an independent prognostic factor for DFS in the present analysis. Intensified local treatment needs to be tested in the context of more efficient concurrent, neoadjuvant, and adjuvant systemic therapy. Although the effect of adjuvant chemotherapy on survival for resected STS has yet to be established [20], distant metastases remain the dominant pattern of progression for high-risk extremity STS [3].

We acknowledge several limitations of our study. First, the treated population (103 patients treated over 26 years) was heterogeneous, receiving different treatment combinations, sequences and doses. Radiation therapy technology and

consensus on gross tumor volume and clinical target volume has also changed over time [21]. Second, we included extremity, trunk and retroperitoneal STS together, although it is currently recognized that there are very specific and unique anatomical challenges relating to the management of recurrence in each of these sites, and for the retroperitoneal site at least, there may be biologic differences in behaviour and prognosis [3]. The fact that anatomic site was not a significant predictor of overall outcomes, is likely a reflection of a number limitation of our clinical data. Finally, it is very difficult to assess the specific contribution of the IOERT treatment component, because this analysis can not compared local sarcoma control with or without intraoperative electron irradiation. Locally recurrent STS (oligorecurrence) is a broad disease category comprising several types of patient and tumor [20]. Oligorecurrence involves a restricted locoregional tumor burden and has been proposed as a common criterion for treatment strategy optimization [20]. Intraoperative radiotherapy is an attractive method of dose escalation for LR-STS with close or positive margins [5]. IORT has several advantages over EBRT, such as more precise delivery of radiation to a surgically identified high-risk area, mobilization of dose-sensitive organs at risk, temporarily out of the radiation boost field, and shortening of overall treatment time (dose-dense radiotherapy). As reported by Azinovic et al. [13] patients receiving adjuvant EBRT in the current analysis had a higher local control rate than patients in whom EBRT was omitted (85% vs 74%). Even more, we observed that not receiving EBRT for the local relapse was associated with an increased likelihood of IOERT in-field relapse. Although most LR-STS tumors recurred within IOERT field (69%), in the present analysis a higher IOERT dose did not improved local control. Novel technologies could potentially make IOERT considerations more influential,

especially in an attempt to induce immune stimulation against sarcomas [22].

Treatment-related toxicity, including that induced by IOERT administered to treat LR-STS, was well tolerated by our 103 patients. The low rate of severe toxic events suggests that a multimodality approach with re-resection and IOERT is feasible without prohibitive long-term side effects. Location-associated risk should be carefully assessed during IOERT administration in order to minimize the irradiated volume. The definition of organs at risk, availability of dose-volume histograms, and estimations of 3D dose distribution play a key role in optimization of IOERT [14]. Detailed planning on the part of the surgeon and radiation oncologist, along with detailed input from the radiologist prior to surgery and from the pathologist at the time of resection, is decisive for dose-escalation strategies within the tumor bed (field-within-field technique). Future clinical research should focus on functional outcome and quality of life.

Figure 1. Kaplan-Meier curves for all 103 patients for local control (A), IOERT in field control (B), disease-free survival (C) and overall survival (D).

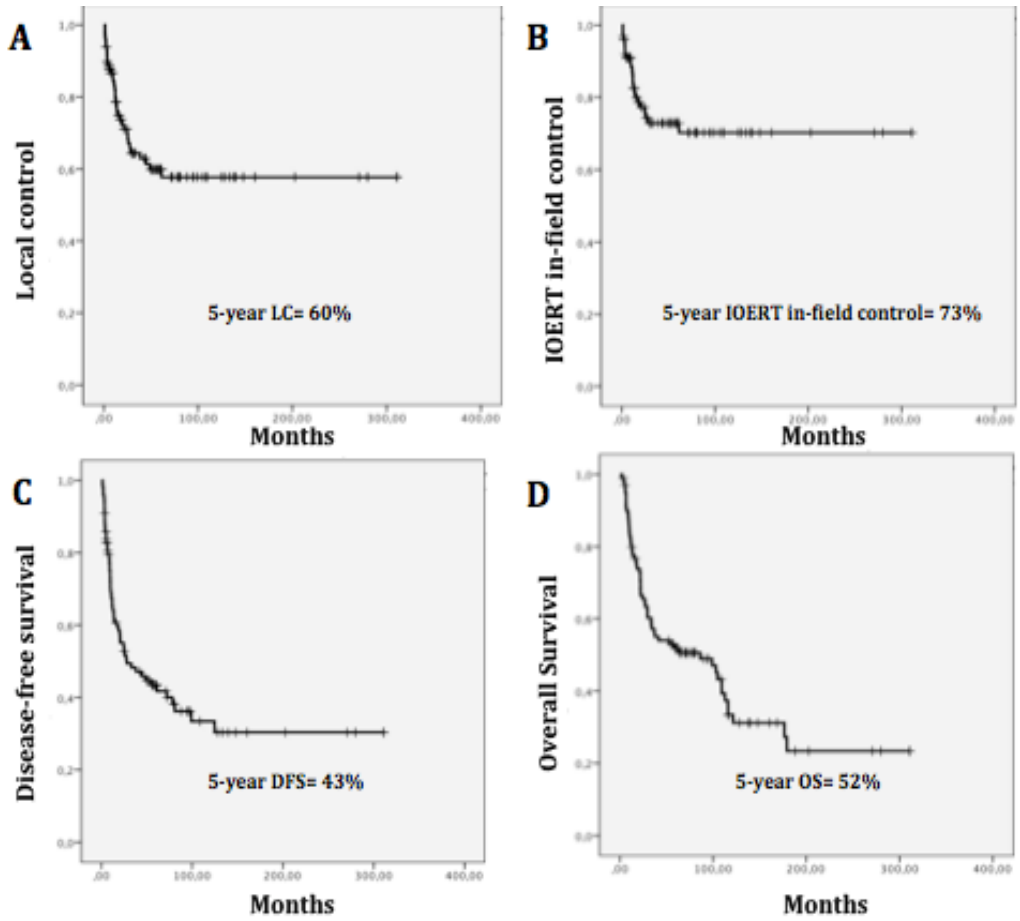


Table 1. Patient, tumor and treatment characteristics

Parameter	Variable	All patients n=103 (%)	EBRT Group n=63 (61%)	No-EBRT Group n=40 (39%)	*p-value*
Patient variables					
Age	***Median age (years)***	53 (23-78)	54 (31-78)	52 (33-76)	*0.89*
Gender	***Male*** ***Female***	40 (39) 63 (61)	26 (41) 37 (59)	14 (35) 16 (65)	*0.71*
Karnofsky Perfomance Status	***< 90*** ***≥ 90***	27 (26) 76 (74)	15 (24) 48 (76)	12 (30) 28 (70)	*0.55*
Time interval from primary to LR (months)	**≥ 24** **< 24**	54 (53) 49 (47)	32 (51) 31 (49)	22 (55) 20 (45)	*0.68*
Pre-surgical variables					
Tumor size	***Median tumor size (cm)***	9 (2-24)	9 (3-24)	10 (3-20)	*0.78*
Tumor Localization	***Extremity*** ***Retroperitoneum*** ***Trunk wall***	44 (43) 34 (33) 25 (24)	32 (51) 18 (28) 13 (21)	12 (30) 16 (40) 12 (30)	*0.19*
Tumor Depth	***Deep*** ***Superficial***	79 (77) 24 (23)	46 (73) 17 (27)	33 (83) 7 (17)	*0.46*
Microscopic surgical specimen					
Histologyc subtype	***Liposarcoma*** **Malignant fibrous histiocytoma** **Leiomyosarcoma** ***Sarcoma NOS*** **Synovial sarcoma** **Other**	38 (37) 19 (18) 11 (11) 8 (8) 8 (8) 19 (18)	21 (33) 14 (22) 5 (8) 6 (10) 7 (11) 10 (16)	17 (43) 5 (13) 6 (10) 2 (3) 1 (2) 9 (14)	*0.53*
Mitosis count	***Low-medium*** ***High***	83 (81) 20 (19)	49 (78) 14 (22)	34 (85) 6 (15)	*0.44*
Necrosis	***Yes*** ***No***	44 (43) 59 (57)	24 (39) 39 (61)	20 (50) 20 (50)	*0.60*
Histologic grade	***I-II*** ***III***	73 (71) 30 (29)	46 (63) 17 (37)	27 (68) 13 (32)	*0.82*
Surgery					
Surgical procedure	***Wide excision*** ***Simple local excision***	64 (62) 39 (38)	40 (63) 23 (37)	24 (60) 16 (40)	*0.78*
Margin status	***R0*** ***R1***	62 (60) 41 (40)	37 (59) 26 (41)	25 (63) 15 (37)	*0.68*
IOERT technical parameters					
IOERT dose (cGy)	**Median IOERT dose (cGy)**	1250 (1000-2000)	1200 (1000-2000)	1250 (1000-2000)	*0.89*
IOERT energy (MeV)	**Median IOERT energy (MeV)**	9 (4-20)	8 (4-20)	9 (4-18)	*0.54*
IOERT applicator size (cm)	**Median IOERT applicator size (cm)**	9 (5-15)	9 (5-15)	10 (5-15)	*0.65*
EBRT-CT treatment					
Adjuvant CT	***Yes*** ***No***	36 (35) 67 (65)	19 (30) 44 (70)	17 (41) 23 (58)	*0.28*
EBRT to the primary tumor	***Yes*** ***No***	31 (30) 72 (70)	17 (27) 46 (73)	14 (35) 26 (65)	*0.21*

IOERT, intraoperative electron-beam radiotherapy; EBRT, external beam radiotherapy; CT chemotherapy; NOS, not otherwise specified

Table 2. Correlations between macroscopic/microscopic pathology characteristics and IOERT technical parameters

Pathology/ IOERT Treatment	**Applicator size**	**IOERT dose (Gy)**	**IORT energy (MeV)**
	Median/ range	**Median/ range**	**Median/ range**
Tmax size (cm)			
2.0-3.0	6/ 5-8	12.5/ 10-20	8/ 4-20
3.1-6.0	9/ 5-9	12.5/ 12.5-20	8/ 4-20
6.1-10.0	9/ 6-10	12.5/ 10-15	9/ 6-20
10.1-15.0	9/ 7-15	12.5/ 12.5-15	9/ 4-20
15.1-24.0	9/ 9-15	12.5/ 10-15	9/ 6-20
Margin resection status			
R0	9/ 5-15	12.5/ 10-20	9/ 4-20
R1	9/ 5-15	12.5/ 12.5-20	9/ 6-20

Multiple field technique procedures in 28 (27%) patients

Tmax= Tumor maximal dimension

Table 3. Univariate analyses of associations between the patient, tumor and treatment with local control, IOERT in-field control, disease-free survival and overall survival

Parameter	Variable	Local Control			IOERT In-field Control			Disease-Free Survival			Overall Survival		
		HR	CI 95%	*P value*	HR	CI 95%	*P value*	HR	CI 95%	*P value*	HR	CI 95%	*P value*
Patient variables													
Gender	***Male*** ***Female***	1.0 0.98	0.50-1.91	*0.95*	1.0 0.80	0.39-1.64	*0.54*	1.0 0.80	0.47-1.36	*0.41*	1.0 0.87	0.33-1.53	*0.45*
Age (years)	***< 50*** ***≥ 50***	1.0 1.09	0.54-2.20	*0.81*	1.0 0.82	0.34-1.97	*0.65*	1.0 1.33	0.76-2.33	*0.32*	1.0 1.59	1.02-2.32	***0.05***
Karnofsky Perfomance Status	***< 90*** ***≥ 90***	1.0 0.61	0.28-1.51	0.34	1.0 0.78	0.34-2.04	0.45	1.0 0.84	0.35-2.10	0.67	1.0 0.88	0.20-2.16	0.71
Time interval from primary to LR (months)	**≥ 24** **< 24**	1.0 2.47	1.03-5.19	**0.04**	1.0 2.95	0.73-7.61	0.17	1.0 3.65	1.21-7.23	**0.01**	1.0 3.18	1.25-6.88	**0.01**
Pre-surgical variables													
Tumor size (cm)	***≤ 10*** ***> 10***	1.0 1.64	0.91-2.94	*0.10*	1.0 1.17	0.58-2.32	*0.67*	1.0 1.14	0.869-1.88	*0.60*	1.0 1.22	0.74-2.23	*0.31*
Tumor Localization	***Extremity*** ***Retroperitoneal*** ***Trunk wall***	1.0 2.26 1.59	 0.85-4.64 0.71-3.10	 *0.14* *0.31*	1.0 2.33 1.33	 0.78.6.09 0.55-3.18	 *0.27* *0.53*	1.0 1.75 1.61	 0.83-3.49 0.79-3.08	 *0.19* *0.23*	1.0 1.35 1.30	 0.74-2.50 0.73-2.33	 *0.33* *0.38*
Tumor depth	***Superficial*** ***Deep***	1.0 1.91	0.74-4.11	0.22	1.0 2.98	0.37-8.75	0.35	1.0 1.21	0.43-3.82	0.41	1.0 1.24	0.37-3.91	0.86
Microscopic surgical specimen													
Histologyc subtype	***Liposarcoma*** ***Others***	1.0 1.24	0.68-2.56	*0.49*	1.0 1.05	0.53-2.08	*0.88*	1.0 1.53	0.90-2.55	0.13	1.0 1.31	0.77-2.23	*0.32*
Mitosis count	***Low-medium*** ***High***	1.0 2.14	0.95-4.81	*0.07*	1.0 1.95	0.78-4.94	*0.16*	1.0 1.60	0.91-2.68	*0.13*	1.0 1.39	0.66-2.89	*0.39*
Necrosis	***Yes*** ***No***	1.0 0.75	0.26-2.41	*0.35*	1.0 1.12	0.54-2.61	*0.88*	1.0 0.51	0.21-1.25	*0.23*	1.0 0.65	0.31-1.19	*0.17*
Histologic grade	***I-II*** ***III***	1.0 1.86	1.02-3.43	***0.05***	1.0 1.55	0.76-3.18	*0.23*	1.0 2.26	1.17-4.36	***0.02***	1.0 1.64	0.96.-2.79	*0.07*
Surgery													
Resection	***Wide resecrion*** ***Local resection***	1.0 1.22	0.61-3.19	*0.30*	1.0 1.91	0.62-5.77	0.29	1.0 1.21	0.43-2.19	0.74	1.0 1.29	0.51-2.87	0.46
Margin status	***R0*** ***R1***	1.0 1.96	1.28-2.95	***0.02***	1.0 1.68	1.03-3.28	***0.05***	1.0 1.58	1.08-2.54	***0.04***	1.0 2.10	1.10-3.80	***0.04***
IOERT technical parameters													
IOERT dose (Gy)	***< 1250*** ***≥ 1250***	1.0 0.93	0.51-1.72	*0.83*	1.0 0.90	0.45-1.82	*0.78*	1.0 1.08	0.65-1.78	*0.77*	1.0 0.93	0.55-1.57	*0.79*
IOERT energy (MeV)	***< 6*** ***≥ 6***	1.0 0.87	0.39-1.65	*0.42*	1.0 0.82	0.23-2.12	*0.71*	1.0 1.10	0.68-1.78	*0.71*	1.0 1.42	0.81-2.17	*0.20*
IOERT applicator size (cm)	***< 9*** ***≥ 9***	1.0 0.92	0.39-1.89	*0.84*	1.0 0.74	0.38-1.44	*0.38*	1.0 0.90	0.46-1.62	*0.75*	1.0 0.78	0.47-1.29	*0.33*
Adjuvant treatment													
EBRT treatment to Primary tumor	***Yes*** ***No***	1.0 0.68	0.38-1.23	*0.21*	1.0 0.61	0.31-1.20	*0.16*	1.0 0.72	0.44-1.19	*0.20*	1.0 0.67	0.31-1.25	*0.32*
EBRT treatment to LR-STS	***Yes*** ***No***	1.0 1.80	1.05-3.17	***0.04***	1.0 1.94	1.0-3.61	***0.05***	1.0 1.28	0.76-2.16	*0.36*	1.0 1.49	0.81-2.45	*0.31*
EBRT re-irradiation	***Yes*** ***No***	1.0 0.75	0.42-2.01	0.55	1.0 0.85	0.54-1.74	0.73	1.0 0.68	0.25-2.09	0.71	1.0 0.92	0.33-2.32	0.88
Adjuvant Chemotharpy	***Yes*** ***No***	1.0 1.18	0.50-2.80	*0.70*	1.0 1.12	0.43-2.89	*0.82*	1.0 1.33	0.71-2.48	*0.38*	1.0 1.18	0.41-2.73	*0.77*

Table 4. Factors associated with local control, IOERT in-field control, disease-free survival and overall survival in multivariate analyses

Parameter	Variable	Local Control			IOERT In-field Control			Disease-Free Survival			Overall Survival		
		HR	CI 95%	*P value*	HR	CI 95%	*P value*	HR	CI 95%	*P value*	HR	CI 95%	*P value*
Patient variables													
Time interval from primary to LR (months)	**≥ 24** **< 24**	-	-	-	-	-	-	1.0 3.87	1.36-7.88	**0.006**	1.0 3.44	1.29-7.08	**0.008**
Microscopic surgical specimen													
Histologic grade	***I-II*** ***III***	-	-	-	-	-	-	1.0 2.41	1.06-4.92	***0.04***	-	-	-
Surgery													
Margin status	***R0*** ***R1***	1.0 1.73	1.06-3.34	***0.04***	-	-	-	1.0 1.72	1.11-2.83	***0.03***	1.0 2.41	1.21-4.21	***0.02***
IOERT technical parameters													
CT treatment													
EBRT treatment to LR-STS	***Yes*** ***No***	1.0 2.12	1.18-3.23	***0.02***	1.0 2.08	1.10-3.64	**0.03**	-	-	-	-	-	-

IOERT, intraoperative electron-beam radiotherapy; EBRT, external beam radiotherapy; CT chemotherapy

Table 5. Series reporting long-term outcomes for patients with soft-tissue sarcomas

	N	Median Follow-up (months)	IORT	Disease status		(Neo)Adjuvant EBRT	Neo (Adjuvant) CT	5-year local Kaplan Meier estimate			
				Primary	Recurrent			IOERT in-field LC	LC	DFS	OS
Zagars et al.[¥]	1225	114 [ÿ]	<1%	84%	16%	100%	33%	NR	83%	60%	71% [Î]
DeLaney et al.[¥]	154	75	10%	87%	13%	100%	15%	NR	76%	47%	65%
Alektiar et al.[†]	32	33	100%	37%	63%	78%	13%	NR	62%	82%	55% [Î]
Petersen et al.[†]	87	42	100%	49%	51%	89%	12%	NR	59%	55%	29% [Î]
Dziewieski et al.[†]	46	20	100%	13%	87%	52%	4%	NR	51%	NR	NR
Krempien et al.[†]	67	30	100%	39%	61%	67%	NR	72%	40%	50%[Ÿ]	28% [Î]
Tran et al.[¥]	50	59	100%	30%	70%	37%	32%	55%	26%	51% [Ÿ]	25% [Î]
Azinovic et al.[§]	45	93 [ÿ]	100%	74%	26%	80%	73%	NR	80% [£]	56% [£]	NR
Oertel et al.[§]	153	33	100%	62%	38%	62%	NR	NR	78%	48% [Ÿ]	77%

IORT, intraoperative radiotherapy

EBRT, external beam radiotherapy

CT, chemotherapy

[¥] Mixed cohorts (retroperitoneum, pelvis, extremity, head & neck and/ or trunk-wall)

[†] Retroperitoneal soft tissue sarcoma only

[§] Extremity soft tissue sarcoma only

[Î] Disease-specific survival

[Ÿ] Distant metastases-free survival

[£] Crude rates

[ÿ] Median follow-up for surviving patients

References.

[1]. Haas RL, Delaney TF, O'Sullivan B. Radiotherapy for management of extremity soft tissue sarcomas: why, when, and where? Int J Radiat Oncol Biol Phys. 2012; 84: 572-80.

[2]. LeVay J, O'Sullivan B, Catton C, et al. Outcome and prognostic factors in soft tissue sarcoma in the adult. Int J Radiat Oncol Biol Phys. 1993; 27:1091-9.

[3]. Delaney TF, Kepka L, Goldberg SI, et al. Radiation therapy for control of soft-tissue sarcomas resected with positive margins. Int J Radiat Oncol Biol Phys. 2007; 67:1460-9.

[4]. Zagars GK, Ballo MT, Pisters PW, et al. Prognostic factors for patients with localized soft-tissue sarcoma treated with conservation surgery and radiation therapy: an analysis of 1225 patients. Cancer. 2003; 97:2530-43.

[5]. Petersen IA, Krempien R, Beauchamp C, et al. Extremity and Trunk Soft-Tissue Sarcomas. In: Gunderson LL, Willet CG, Calvo FA, Harrison LB. Intraoperative irradiation techniques and results. Current Clinical Oncology. 2nd edition. Humana Press, Springer New York Heidelberg. 2011:387-405.

[6]. Alektiar KM, Hu K, Anderson L, et al. High-dose-rate intraoperative radiation therapy (HDR-IORT) for retroperitoneal sarcomas. Int J Radiat Oncol Biol Phys. 2000;47:157–163.

[7]. Petersen IA, Haddock MG, Donohue JH, et al. Use of intraoperative electron beam radiotherapy in the management of retroperitoneal soft tissue sarcomas. Int J Radiat Oncol Biol Phys. 2002; 52:469–475.

[8]. Krempien R, Roeder F, Oertel S, et al. Intraoperative electron beam therapy for primary and recurrent retroperitoneal soft-tissue sarcoma. Int J Radiat Oncol Biol Phys. 2006;65:773–779.

[9]. Dziewirski W, Rutkowski P, Nowecki ZI, et al. Surgery combined with intraoperative brachytherapy in the treatment of retroperitoneal sarcomas. Ann Surg Oncol. 2006;13: 245–252.

[10]. Tran PT, Hara W, Su Z, et al. Intraoperative radiation therapy for locally advanced and recurrent soft-tissue sarcomas in adults. Int J Radiation Oncology Biol Phys. 2008; 72: 1146–1153.

[11]. Haddock MG, Petersen IA, Pritchard D, et al. IORT in the management of extremity and limb girdle soft tissue sarcomas. Front Radiat Ther Oncol. 1997;31:151–152.

[12]. Oertel S, Treiber M, Zahlten-Hinguranage A, et al. Intraoperative electron boost radiation followed by moderate doses of external beam radiotherapy in limb-sparing treatment of patients with extremity soft-tissue sarcoma. Int J Radiat Oncol Biol Phys. 2006;64:1416-23.

[13]. Azinovic I, Martinez Monge R, Javier Aristu J, et al. Intraoperative radiotherapy electron boost followed by moderate doses of external beam radiotherapy in resected soft-tissue sarcoma of the extremities. Radiother Oncol. 2003;67:331–337.

[14]. Pascau J, Santos Miranda JA, Calvo FA, et al. An innovative tool for intraoperative electron beam radiotherapy simulation and planning: description and initial evaluation by radiation oncologists. Int J Radiat Oncol Biol Phys. 2012; 83:287-295.

[15]. Cox JD, Stetz J, Pajak TF. Toxicity criteria of the Radiation Oncology Group (RTOG) and the European Organization for Research and Treatment of Cancer (EORTC). Int J Radiat Oncol Biol Phys. 1995; 31:1341–1346.

[16]. Sampo M, Tarkkanen M, Huuhtanen R et al. Impact of the smallest surgical margin on local control in soft tissue sarcoma. Br J Surg. 2008;95:237-43.

[17]. Kawaguchi N, Matumoto S, Manabe J. New method of evaluating the surgical margin and safety margin for musculoskeletal sarcoma, analysed on the basis of 457 surgical cases. J Cancer Res Clin Oncol. 1995;121:555-63.

[18]. Pervaiz N, Colterjohn N, Farrokhyar F, et al. A systematic meta-analysis of randomized controlled trials of adjuvant chemotherapy for localized resectable soft-tissue sarcoma. Cancer. 2008;113:573-81.

[19]. Rimner A, Brennan MF, Zhang Z, et al. Influence of compartmental involvement on the patterns of morbidity in soft tissue sarcoma of the thigh. Cancer. 2009;115:149-57.

[20]. Weichselbaum RR, Hellman S. Oligometastases revisited. Nat Rev Clin Oncol. 2011;8:378-82.

[21]. Wang D, Bosch W, Roberge D, et al. RTOG sarcoma radiation oncologists reach consensus on gross tumor volume and clinical target volume on computed tomographic images for preoperative radiotherapy of primary soft tissue sarcoma of extremity in Radiation Therapy Oncology Group studies. Int J Radiat Oncol Biol Phys. 2011;81:525-8.

[22]. Finkelstein SE, Iclozan C, Bui MM, et al. Combination of external beam radiotherapy (EBRT) with intratumoral injection of dendritic cells as neo-adjuvant treatment of high-risk soft tissue sarcoma patients. Int J Radiat Oncol Biol Phys. 2012;82:924-32.

4. Discusión

4. DISCUSIÓN.

4.1. CUMPLIMIENTO DEL ESQUEMA TERAPÉUTICO.

La práctica totalidad de los pacientes (92% casos) culminaron de forma satisfactoria el tratamiento radioterápico, recibiendo una dosis total de al menos 45 Gy los pacientes sin irradiación previa y 30,6 Gy los pacientes sometidos a re-irradiación. Por otro lado, la mediana de duración del tratamiento con irradiación fue de 36 días para el grupo sin irradiación previa y 20 días para los pacientes sometidos a re-irradiación. Estos datos ponen de manifiesto un adecuado cumplimiento del tratamiento radioterápico en los grupos de estudio y ratifican la tendencia actual hacia la intensificación terapéutica (incluyendo segmentos de re-irradiación) en este grupo de pacientes.

La administración de quimioterapia radiosensibilizante fue reducida o suspendida en el 10% de los pacientes con oligo-recurrencia rectal y , en un 12% de los pacientes con oligo-recurrencia ginecológica. El cumplimiento íntegro del tratamiento quimioterápico se pudo llevar a cabo en el 93% de los casos con oligo-recurrencia rectal y en el 90% de los pacientes con oligo-recurrencia ginecológica. La resección quirúrgica se realizó en una mediana de 36 días antes o después de recibir el tratamiento con radioterapia externa, siendo cifras comparables y consistentes entre los tres grupos de estudio. En un total de 132 pacientes pudo llevarse a cabo una resección radical con márgenes microscópicos negativos. Esto supone un índice de resecabilidad completa del 59%. Por último, es importante señalar que el 44% de los pacientes recibieron quimioterapia adyuvante posterior a la cirugía. En conclusión, se puede afirmar que esta estrategia de innovación terapéutica en rescate de intención radical, presenta un excelente índice de cumplimiento asistencial que no condiciona la posibilidad de completar de forma

satisfactoria todos los componentes multidisciplinares de un abordaje tan complejo como requiere el cáncer oligo-recurrente candidato a tratamiento activo.

4.2. TOXICIDAD DEL ESQUEMA DE TRATAMIENTO Y MORBI-MORTALIDAD POSTOPERATORIA.

Los resultados de toxicidad relacionada con el tratamiento, la tolerancia clínica integral y las tasas de complicaciones post-quirúrgicas sugieren que un enfoque multimodal que incluye un componente de RIO y RTE es factible, con riesgos de eventos tóxicos asumibles y sin efectos previsibles prohibitivos a largo plazo. Este dato coincide con la experiencia de estudios similares y con otras publicaciones que afirman que el tratamiento intensivo en equipos multidisciplinares expertos minimizan los riesgos [60]. Por lo tanto, parece aceptable afirmar que la incorporación de un programa de tratamiento multidisciplinar intensivo no supone un incremento en el índice de morbi-mortalidad postoperatoria en comparación con los abordajes tradicionales no intensivos (sin componente radioterápico) y presenta valores comparables con otras experiencias estratégicas similares en grupos expertos [60]. Las causas de toxicidad aguda y crónica fueron consideradas como multifactoriales y relacionadas con las características individuales del paciente [61].

4.2.1. CÁNCER OLIGO-RECURRENTE RECTAL.

En total, 25 pacientes (42 %) presentaron toxicidad aguda grado ≥ 3 [fístula gastrointestinal (n=4, grado 3), absceso de partes blandas (n=1, grado 3), infección de herida operatoria (n=3, grado 3; n=2, grado 5), neuropatía periférica (n=4, grado 3; n=1, grado 4), cardíaca (n=4, grado 3; n=1, grado 5), pulmonar (n=5, grado 3)]. Doce pacientes (20%) experimentaron toxicidad crónica grado ≥ 3 [gastrointestinal (n=4, grade 3; n=2, grade 4); neurológica (n=3, grade 3; n=3,

grade 4)]. La mortalidad perioperatoria fue de un 5% [infección de herida operatoria-sepsis (n=2); cardíaca (n=1)]. En relación a las complicaciones perioperatorias, se observa que los pacientes tratados con cirugía extendida presentan más frecuentemente complicaciones que: los tratados con cirugía de rescate no-extendidas (descarga, resección atípica, etc.) [73.7% (n=28) versus 45.5% (n=10); p=0.03)]; los procedimientos quirúrgicos de mayor duración [mediana de 365 minutos (rango, 145-750 minutos) versus 260 minutos (rango, 100 vs. 465 minutos); p=0.02)]; la prolongación de la estancia en la unidad de cuidados intensivos [mediana de 2 días (rango, 0-18 días) versus 0 días (rango, 0-2 días); p=0.004)] y un mayor tiempo de hospitalización [mediana de 17 días (rango, 1-156 días) versus 10 días (rango, 1-50 días); p=0.005)]. En relación a la mortalidad perioperatoria no se observaron diferencias [7.8% (n=3) versus 0% (n=0); p=0.18].

4.2.2. CÁNCER OLIGO-RECURRENTE GINECOLÓGICO.

Un total de 14 pacientes (39 %) desarrollaron toxicidad aguda grado ≥ 3 y 8 pacientes (23 %) toxicidad crónica grado ≥ 3. La mortalidad relacionada con el tratamiento fue de 2.9% (n=1, sepsis de origen en infección de herida operatoria). No se observaron diferencias en mortalidad perioperatoria entre los pacientes tratados por recurrencias pélvicas y paraaórticas [3% (n=1) vs. 0% (n=0); p=0.65)].

4.2.3. CÁNCER OLIGO-RECURRENTE DE SARCOMA DE PARTES BLANDAS.

En total, 16 pacientes (16%) presentaron toxicidad aguda ≥ 3 [reacciones cutáneas severas (n=7, grado 3]; alteraciones de cicatrización de herida quirúrgica(n=5, grado 3; n=4, grado 4)]. Las reacciones cutáneas severas y los trastornos de cicatrización de heridas se observaron más frecuentemente en pacientes con

sarcomas oligo-recurrentes de extremidad (n=3, grade 3) y tronco (n=2, grade 3; n=2, grade 4). Trece pacientes (13%) desarrollaron toxicidad crónica grado ≥ 3 [neuropatía (n=6, grade 3); necrosis/fístula/ulcera (n=3, grade 3), y linfedema crónico severo (n=7, grade 3).

La neuropatía, necrosis/fístula/ulcera y el linfedema crónico severo fueron observados con mayor frecuencia en pacientes con sarcoma oligo-recurrente retroperitoneal (n=3, grade 3), de tronco (n=2, grade 3) y extremidad (n=7, grade 3), respectivamente. No se identificó diferencia significativa en toxicidad aguda o crónica entre los pacientes que recibieron y los que no recibieron radioterapia externa integrada en el tratamiento de rescate.

4.3. FACTORES PREDICTIVOS DE RESPUESTA/CONTROL Y TIEMPO A PROGRESIÓN Y SUPERVIVENCIA.

El concepto de oligometástasis implica una carga tumoral restringida y un patrón evolutivo indolente, por lo que se ha propuesto a este grupo de pacientes como candidatos a estrategias de tratamiento intensificado mediante la combinación de cirugía, radioterapia y quimioterapia [1]. La categoría de oligo-recurrencia loco-regional es heterogénea e incluye varios subtipos de enfermedad oncológica [6]. Sin embargo, los pacientes con oligo-recurrencia loco–regional presentan una carga tumoral limitada y se ha propuesto como un criterio común para la optimización de la estrategia de terapéutica de rescate [7]. Se ha observado y documentado que algunos pacientes en esta situación particular, podrían beneficiarse de una terapia local intensificada [11].

Reconocemos varias limitaciones en el presente estudio. La muestra clínica y patológica analizada es heterogénea y el período evaluado prolongado, habiendo

sido tratados en más de 16 años consecutivos para los tumores de recto, en 18 años para los tumores ginecológicos y en 26 años para los sarcomas de partes blandas. Se asume con evidencia académica que la cirugía y oncología han actualizado y mejorado su eficiencia clínica en los últimos 25 años. Aunque se identifica una asociación entre el tratamiento con radioterapia externa y el control local, la presencia de un sesgo de selección en los pacientes tratados con una dosis integral superior no se puede descartar. Los pacientes que no recibieron RTE tenían mayores reservas relacionadas con el riesgo de toxicidad por re-tratamiento o existía una mayor incertidumbre clínica relacionada con la eficacia terapéutica oncológica final. Además , es difícil evaluar la contribución específica del componente de RIO, debido a que en el presente análisis no se compararon grupos con o sin RIO. Sin embargo los elementos metodológicos del componente de RIO han sido meticulosamente analizados en el contexto de su integración en el manejo multimodal de la enfermedad oligo-recurrente.

4.3.1. CÁNCER OLIGO-RECURRENTE RECTAL.

Nuestros resultados relevantes se pueden resumir de la siguiente manera. En primer lugar, encontramos que la resección quirúrgica extendida compensa ciertas características adversas de RLR . En segundo lugar, se observa que no agregar RTE a la cirugía y RIO en pacientes con oligo-recurrencia loco- regional de tumor primario rectal se asoció significativamente con un aumento del riesgo de RLR. Además, el valor del uso de RTE mantiene significación estadística cuando los pacientes con resección R0 y con fragmentación tumoral se analizaron por separado. Por último, se identifica que los pacientes sin fragmentación del tumor tenían resultados oncológicos más favorables a largo plazo.

Aunque el número de estudios que evalúan cirugía, RIO y RTE en pacientes con oligo-recurrencia locoregional de tumor primario rectal es limitado, los principales resultados del presente análisis (CLR a 5 años de 44% y SG a 43%) son comparables con los descritos en la literatura (CLR a 5 años 30%-75% y SG a 5 años 20%-50%) [57]. Haddock et al. [57] comunicó la mayor experiencia institucional de tratamiento de rescate con RIO para pacientes con oligo-recurrencia loco-regional de tumores primarios colorectales (n=607). En su análisis no se proporcionan datos detallados sobre la región anatómica de recurrencia susceptible de rescate quirúrgico. El resultado más favorable se detectó en las recurrencias de primarios de colon (vs. recto) (supervivencia a 5 años de 34% vs. 28 %, p=0.07). Kusters et al. [52] analizó 170 pacientes sometidos a tratamiento multimodal con RTE preoperatoria con quimioterapia sensibilizante, cirugía y RIO. Los peores resultados se concentraban en los pacientes con recurrencias presacras [28% resecciones completas y 19% de supervivencia a 5 años (p = 0.03)]. Alternativamente, se observaron los resultados más favorables en los pacientes con recurrencias anastomóticas [77% de resecciones R0 y 60% de supervivencia a los 5 años (p=0.04)]. En un análisis anterior Calvo et al. [62] evaluó la factibilidad y los resultados a largo plazo de pacientes con oligo-recurrencia extrapélvica (n=28) tratados con cirugía y RIO. Con una mediana de tiempo de seguimiento de 39 meses, observó que los pacientes con un con afectación por tumor mayor al 50% de los fragmentos remitidos a estudio anatomopatológico presentaron mayor riesgo de RLR (38% vs. 9%, p=0.02). En el análisis actual, el no presentar fragmentación tumoral se asocia a mejores resultados de control oncológico a largo plazo.

Varios estudios han demostrado que la re-irradiación pélvica con una dosis total de RTE moderada (<35 Gy) es tolerable, con tasas moderadas de toxicidad tardía y que su efecto promueve el control local [63]. En el presente análisis, los pacientes re-irradiados (n = 7) no presentaron peores resultados de supervivencia, probablemente porque 5 de 7 pacientes tuvieron resecciones R0, por lo que es difícil detectar una ventaja ante los pacientes sin re-irradiación (n = 21). Valentini et al. [63] ha identificado que en pacientes con oligo-recurrencia loco-regional de tumor primario rectal que habían recibido previamente radioterapia externa pélvica la supervivencia global alcanzó a 5 años el 39%, a pesar de que el 87.4% de los pacientes se extendían hasta la pared lateral (resecciones R0, 35%; SG a 5 años de 64%).

En el presente análisis observamos que los pacientes que recibieron RTE pre-operatoria obtienen los mejores resultados oncológicos [64]. Pacelli et al. [64] comunicó en un análisis de pacientes con resecciones potencialmente curativas (R0 a R1) que la quimio-radioterapia preoperatoria mejoraba la SG a 5 años (44,6 vs 25,8 %, p = 0,012). La secuencia óptima de tratamientos multimodales y la contribución de un componente de RTE y RIO en este complejo escenario clínico es controvertida y merece nuevos análisis expertos basados en el rescate adaptado al riesgo individual.

4.3.2. CÁNCER OLIGO-RECURRENTE GINECOLÓGICO.

Nuestros resultados más relevantes se pueden resumir de la siguiente manera . En primer lugar , se observó que no añadir RTE a la cirugía y RIO se asoció a un incremento en el riesgo de re-recurrencia local, metástasis y muerte. En segundo lugar , los pacientes con oligo-recurrencias para-aórticas presentaron un mayor riesgo de metástasis en comparación con los pacientes con oligo-recurrencias

pélvicas. En tercer lugar, hemos observado que los pacientes con un intervalo de tiempo entre el diagnóstico del tumor primario y la RLR < 24 meses, presentaron un mayor riesgo de re-recidiva local y muerte . Por último, los pacientes sin fragmentación tumoral presentaron un menor riesgo de re-recurrencia local.

Varias instituciones expertas en cirugía y RIO han analizado cohortes mixtas con amplios criterios de inclusión y resultados comparables al presente análisis. La evaluación de resultados no seleccionó pacientes por el origen del tumor primario, ni modalidades de tratamiento en el abordaje inicial radical, ni por volumen o extensión de la recurrencia tumoral y, asimismo, se incluyeron pacientes con oligo-recurrencia pélvica y para-aórtica.

La discriminación entre los tumores primarios localmente avanzados y loco-regionalmente oligo-recurrentes es relevante porque la supervivencia (SG a 10 años, 14 vs. 67 %, p < 0,001) y el control local (control en campo de RIO, 47 vs. 93 %, p < 0,001) de los pacientes con tumores primarios es significativamente superior [44].

Con frecuencia se ha informado que existe una asociación entre la realización de una resección quirúrgica completa (R0/R1 resección) y un control local y supervivencia superiores [65]. En un análisis de la Clínica Mayo [65] se evaluaron 148 pacientes (84 % oligo-recurrentes) con tumores ginecológicos tratados con resección quirúrgica máxima completada con RIO (76 % RTE). El CLR y la SG a 5 años fueron de 60 % y 27 %. Los pacientes con resecciones R2 tuvieron una supervivencia significativamente menor que los pacientes con resecciones R0/R1 (SG a 5 años, 13 vs. 31 %, p = 0.01). La tasa de metástasis a distancia a 5 años fue menor en los pacientes con resecciones R0/R1 (49%) respecto a R2 (58 %), pero el CLR a 5 años fue de 74 % para los pacientes con resecciones R2 frente a 58%

para los pacientes con resecciones R0/R1. El elevado control local observado en pacientes R2 puede ser explicado por la mayor tasa de metástasis a distancia con la muerte precoz sin permitir que la recidiva local se manifestara clínica o radiológicamente. Aubey et al. [58] analizó 56 pacientes tratados con resección radical seguida de RIO con braquiterapia de alta tasa de dosis. Con una mediana de seguimiento de 11,4 meses , la tasa de supervivencia a los 2 años para los pacientes con resecciones R2 fue de 20 % frente al 60% para aquellos con resecciones R0/R1 ($p < 0,01$). Mahe et al. [46] ha comunicado en un análisis multi-institucional restringido a centros franceses, que no observó ninguna diferencia en la tasa de metástasis a distancia al estratificar por márgenes de resección. Sin embargo, dado que la frecuencia de CLR en el grupo con márgenes R2 fue de 16%, es probable que muchos de estos pacientes fallecieran de la progresión de la enfermedad local antes de que las metástasis a distancia fueran detectables.

En la experiencia que se analiza en este trabajo el uso de una estrategia multimodal con componente de RIO ha modificado aparentemente la planificación y extensión de la resección quirúrgica (ningún paciente tenía enfermedad residual macroscópica). En lo que se refiere a la extensión de la resección quirúrgica (R0 vs R1) no se evidencian diferencias en CLR, ni SG. En la experiencia de la Clínica Mayo [65], se comunicó una supervivencia inferior para los pacientes con un intervalo libre de enfermedad ≤ 2 años en comparación con aquellos con un intervalo > 2 años (SG a 5 años, 14 vs 35 %, p=0.002). Nuestra observación en pacientes con un intervalo <24 meses con resultados globales más comprometidos que los pacientes con un intervalo ≥ 24 meses es consistente con los hallazgos mencionados anteriormente.

La contribución clínica al incluir un componente de RTE en un tratamiento de rescate multimodal es incierta. Pacientes previamente irradiados (se asume que tienen una biología adquirida de radioresistencia) se han asociado a resultados evolutivos adversos. Sin embargo, esta observación no ha sido confirmada en la evaluación actual ni en otras experiencias publicadas previamente [65]. La serie de la Clínica Mayo de 25 pacientes con cáncer de endometrio oligo-recurrente [66], mostró que el empleo de RTE se asoció con una mejor supervivencia ($p = 0.019$). En la serie de la Clínica Mayo de 89 pacientes con cáncer de cuello uterino [oligo-recurrentes (83 %) y primarios localmente avanzados (17 %)] tratados con RIO después de la resección quirúrgica (69 % recibió RTE) [67], el análisis multivariante identificó la exenteración pélvica y la RTE con control local superior. En consonancia con este hallazgo encontramos que los pacientes sin tratamiento de RTE tuvieron resultados globales inferiores al compararlos con los que recibieron RTE. Como datos originales y de singular interés cabe destacar que los pacientes con fragmentación tumoral y resecciones R0 tratados con RTE tenían mejor control local que los que no recibieron RTE. Sin embargo, definir la secuencia óptima de tratamiento junto con la contribución de los componentes de RTE y/ o RIO permanecen como elementos de interpretación controvertidos y pendientes de nuevos estudios.

Se ha informado que los pacientes con oligo-recurrencia exclusivamente en la región para-aórtica pueden lograr un excelente control local y supervivencia después de terapia de rescate [9] . En el análisis actual, aunque los pacientes con oligo-recurrencia para-aórtica aislada presentaron un control local y supervivencia comparables con los pacientes con oligo-recurrencia pélvica, se observa una mayor incidencia de re-metastatización, lo que sugiere un potencial de migración celular

superior (exhibido al poderse considerar a este sub-grupo como oligo-recurrencia regional en sí mismo).

4.3.3. CÁNCER OLIGO-RECURRENTE DE SARCOMA DE PARTES BLANDAS.

Hasta donde llega nuestro conocimiento actualizado, este es el primer estudio que se centra en los resultados a largo plazo observados en pacientes con oligo-recurrencia local de sarcoma de partes blandas tratados con un componente de RIO, después de la resección quirúrgica, asociado o no a RTE. Nuestros hallazgos más relevantes se pueden resumir de la siguiente manera. En primer lugar, se observó que la combinación de RTE, resección quirúrgica y RIO se asoció significativamente con una disminución en la probabilidad de RLR y recaída dentro del campo de RIO. En segundo lugar, se encontró que los pacientes con un intervalo de tiempo < 24 meses entre el diagnóstico del tumor primario y la oligo-recurrencia local presentan una mayor probabilidad de metástasis y muerte. Finalmente, los pacientes con márgenes microscópicos positivos presentan peores resultados oncológicos globales.

Varias instituciones expertas en cirugía asociada a RIO con criterios de inclusión abiertos a individualización y adaptación al riesgo (cohortes mixtas de pacientes con primarios localmente avanzados y oligo-recurrencias locales; sarcomas de extremidades, tronco o centrales y retroperitoneales), en programas de rescate multidisciplinares, han comunicado resultados comparables a los descritos en el presente análisis. La singularidad del presente trabajo consiste en la inclusión exclusiva de pacientes con oligo-recurrencias locales. La selección no se basó de forma excluyente en el espacio anatómico original del sarcoma, el volumen de la recurrencia o las modalidades de tratamiento iniciales. Sin embargo, en todos los casos se confirmaron márgenes cercanos (< 1 cm) o positivos (R1), lo que implica

una resección técnicamente difícil y un pronóstico oncológico adverso [33]. La discriminación entre un sarcoma primario localmente avanzado y un sarcoma localmente oligo-recurrente es importante, ya que los pacientes oligo-recurrentes se asocian con adversidad evolutiva (neoplasia resistente a tratamientos previos y alteración anatómica por cirugía de intención radical previa) [33]. Varios grupos han desarrollado con éxito estrategias de tratamiento combinado (RIO y resección quirúrgica) en cohortes mixtas (primarios y recurrentes) de pacientes (control local a 5 años, 60-80 %) [33]. Aunque está ampliamente aceptado que la calidad del margen quirúrgico es de suma importancia en la promoción del control local, las características específicas que constituyen un margen quirúrgico adecuado no están totalmente definidas. Se ha insistido reiteradamente que los márgenes quirúrgicos positivos son un factor pronóstico desfavorable [68, 69]. Oertel et al. [68] comunicó un control local y SG a 5 años de 78% y 77 %, en la mayor experiencia institucional de RIO en pacientes con sarcoma de partes blandas publicada hasta la actualidad (n = 153, 32% oligo-recurrentes). Se observó que el control local fue más favorable para los pacientes con resecciones completas (CL a 5 años 85% vs. 60%, p=0.03). Azinovic et al. [69] analizó 45 pacientes con sarcomas de extremidades (42 % oligo-recurrentes) tratados con RTE postoperatoria y RIO. El control local a 5 años fue de 87 %, y el estado del margen (márgenes negativos o cercanos vs. márgenes positivos, p=0.04) afectó significativamente el control local. En el análisis actual, la presencia de márgenes de resección positivos microscópicamente se asoció significativamente con resultados mas comprometidos a largo plazo.

El grado histológico es un factor predictivo independiente para el desarrollo de metástasis en los pacientes con sarcoma de partes blandes [33]. En el modelo de

sarcoma oligo-recurrente también confirma que el grado histológico es un factor pronóstico independiente de SLE.

Aunque el efecto de la quimioterapia adyuvante en la supervivencia no está totalmente dilucidado en pacientes con sarcoma de partes blandas [33], el patrón dominante de progresión en este grupo de enfermos sigue siendo el desarrollo de metástasis a distancia. Es importante considerar que el potencial del tratamiento local intensificado tiene que ser evaluado en el contexto de tratamientos sistémicos concurrentes, neo-adyuvantes y adyuvantes, para aspirar a un mayor índice terapéutico.

Azinovic et al. [69] observó que los pacientes que recibieron RTE adyuvante presentaron un control local superior que los pacientes que no recibieron RTE (85% vs. 74%). En el presente análisis, identificamos que los pacientes que no recibieron RTE no sólo presentaron un riesgo más elevado de recidiva local, sino que también presentaron un mayor riesgo de recidiva dentro del campo de RIO. Aunque la mayoría de las re-recurrencias locales se desarrollaron dentro del campo sobreimpresionado con RIO (69%), no se objetivó que una modesta escalada de dosis superiores a 12. 5 Gy se asociara con la promoción del control local.

El compromiso de radicalidad quirúrgica y el riesgo asociado a la ubicación de un sarcoma oligo-recurrente se debe evaluar con esmero e individualización durante la administración de la RIO y RTE con el fin de reducir al mínimo el volumen anatómico irradiado. La definición de órganos de riesgo , la disponibilidad de histogramas de dosis-volumen y las estimaciones de la distribución dosimétrica 3D deben contribuir a la optimización metodológica de la RIO. La planificación detallada y compartida por parte del cirujano y el oncólogo radioterápico, junto

con la integración multidisciplinar del radiólogo y patólogo en el momento de la resección, son elementos decisivos para promover estrategias de escalada de dosis en el lecho tumoral (técnicas de campo dentro del campo o subvolúmenes de sobreimpresión).

El escenario hospitalario de los programas oncológicos que contienen la técnica de RIO basa su excelencia en una actividad interdisciplinar innovadora y en la relación multi-profesional coordinada y exigente. El paciente con cáncer oligo-recurrente constituye un reto clínico de alta complejidad médica que merece tener opción a ser evaluado por grupos oncológicos expertos en rescate multidisciplinar intensificado.

4.4. INVESTIGACIÓN Y DESARROLLO.

4.4.1. ANÁLISIS CRÍTICO DE LA CLASIFICACIÓN ACTUAL.

Todavía en el siglo 21 el estado metastático y/ o recurrente se considera como la etapa final en la vida del paciente oncológico. La diseminación generalizada de múltiples lesiones en diversos órganos es la imagen que un oncólogo evoca como futuro inmediato cuando se diagnostica una recurrencia aparentemente solitaria. Para el paciente y para el médico, la ilusión por buscar opciones de superación de la oligo-metástasis y/ o oligo-recurrencia es contraria a la intuición de un desenlace fatal. Sin embargo numerosas instituciones han generado una experiencia considerable sobre este intrigante perfil clínico [6-13]. El potencial para curar el estado de oligo-recurrencia se ha consolidado en la última década [6]. Los pacientes pueden ser abordados mediante escisión quirúrgica , ablación mediante radiocirugía estereotáxica , fármacos radiomarcados o guiados a dianas biológicas específicas o quimioterapia citotóxica. Sin embargo, la realidad

demuestra que hay más muertes por cáncer metastático cada año que el número total de pacientes con oligo-metástasis y/ o oligo-recurrencia supervivientes a largo plazo, si se combinan todas las localizaciones y primarios publicados durante el siglo pasado hasta la actualidad [6]. El sistema de clasificación de las oligometástasis y/o oligo-recurrencias (al igual que la estadificación TNM) se basa sobre un modelo temporal, que supone una propagación por contigüidad de enfermedad que se mide cronológicamente (determinismo temporal). La precisión predictiva del sistema depende de que los pacientes se presenten en todo el rango temporal de la enfermedad. Debido a que la precisión predictiva del sistema depende de la progresión en el tiempo de los tumores, cualquier evento que reduzca la dimensión temporal reduce la precisión del sistema de clasificación, limitando la exactitud de este sistema a través de la compresión. Además, la viabilidad del modelo temporal se ha cuestionado por datos empíricos; por ejemplo, algunos pacientes con tumores de pequeñas dimensiones, sin evidencia de afectación a distancia, progresan y mueren de su enfermedad antes que otros pacientes con mayor carga tumoral o enfermedad más avanzada [11]. Si se clasifica un paciente con un mejor pronóstico en un grupo con un peor pronóstico, el resultado será un error mayor en estimación de potencial evolutivo. Se suma al problema de compresión por etapas, la carencia de este sistema de clasificación al no proporcionar información pronostica en base a tratamientos neo- y/o adyuvantes. Desde su descripción inicial parece un sistema con sentido quirúrgico restrictivo. El orden de los pacientes asume que todos los pacientes serán sometidos a cirugía sin ningún otro tratamiento complementario (no tiene en cuenta que los pacientes recibieron quimioterapia y/ o radioterapia). Por lo tanto,

efectos en la supervivencia relacionadas con estas terapias no se reflejarán en la predicción evolutiva de la clasificación.

Es necesario impulsar una clasificación que permita racionalizar los elementos relacionables con otros factores como los tratamientos y responder al menos a las siguientes preguntas claves: 1) ¿Se necesita alguna terapia para este paciente: es decir, es la historia natural de la enfermedad lo suficientemente adversa como para justificar tratamiento activo? 2) Si el paciente tiene un pronóstico ominoso sin tratamiento, que terapia, combinación de terapias, o sucesión de terapias proporcionará la mayor probabilidad de supervivencia y la mejor calidad de vida? Este punto requiere descubrir nuevos abordajes y encontrar factores pronósticos específicos que permitan afinar en la predicción de la respuesta terapéutica individual. 3) ¿Qué efectos tóxicos o complicaciones de estos abordajes de rescate experimentaran los pacientes con cada componente terapéutico? ¿Existen medidas que puedan mitigar o eliminar estos efectos secundarios?

Estas preguntas no pueden ser respondidas por el actual sistema de clasificación. La medicina personalizada requiere para alcanzar relevancia clínica, que los biomarcadores moleculares y/o metabólicos se puedan integrar en el sistema actual [4] para proporcionar una predicción individual de tolerancia terapéutica y supervivencia. La futura utilidad de este sistema de clasificación depende de su capacidad de asumir el aumento en la detección de pacientes oligo-metastáticos y/o oligo-recurrentes, el descubrimiento e incorporación en la practica clínica de nuevas terapias, y el uso de biomarcadores noveles [metabólicos y moleculares (genómica, proteómica y/ o metabolómica)]. Debemos pasar de un modelo de determinismo temporal a uno de determinismo biológico. En el que no se define al paciente según la etapa de detección, sino más bien por las características

moleculares del tumor y de los pacientes. El determinismo biológico considera que la localización anatómica de la enfermedad en la detección está más relacionado con métodos de diagnóstico morfológico a nivel macroscópico disponibles, que con el propio tumor.

4.4.2. BIOMARCADORES MOLECULARES.

La perspectiva sobre el estado de oligo-recurrencia oncológica ha cambiado drásticamente con el desarrollo y sofisticación de los métodos de imagen y marcadores moleculares. El progreso experimentado en medicina clínica ha permitido al oncólogo refinar el diagnóstico y seguimiento de pacientes asintomáticos.

El hallazgo de una lesión metastásica puede ser metacrónica (después de que el tumor primario ha sido tratado) o sincrónica (presente en el diagnóstico inicial de la enfermedad neoplásica). Aunque es habitual que las lesiones metastásicas se manifiesten después del tratamiento del tumor original, la mayor precisión diagnóstica ha aumentado significativamente la detección de diseminación metacrónica en nivel subcentimétrico y celular mediante tecnología de imagen metabólica y molecular o la determinación de células tumorales circulantes [11].

Los focos metastásicos tienen rasgos histopatológicos similares al tumor primario y raras veces se transforman groseramente en otro fenotipo (esto es, tumores epidermoides no se convierten en adenocarcinomas). El modelo de expansión morfológico "esferoide" se asume que simula biológicamente el devenir de las micrometástasis y es el precursor mas aceptado en investigación básica de la historia natural del proceso de oligometástasis y/ o oligo-recurrencia [70].

Los sistemas experimentales han señalado que el aumento de la malignidad y de la capacidad migrante es un proceso de múltiples pasos asociado a inestabilidad

genética [70]. Los momentos claves incluyen: (1) fuga del tumor primario por intravasación en la circulación; (2) supervivencia en la circulación; (3) arresto vascular en un nuevo órgano; (4) fuga de la circulación, extravasación; (5) migración en el espacio intersticial en el nuevo sitio e iniciación de crecimiento en un microesferoide; (6) desarrollo neovascular para mantener crecimiento y proliferación continuada.

El proceso de formación de metástasis puede ser entendido como una cascada continua de eventos biológicos en relación con células cancerosas circulantes. Debido a que sólo un número limitado de émbolos celulares se transforma en una metástasis y/o recurrencia clínicamente relevante, el proceso de colonización celular es considerado biológicamente ineficiente [71]. Alternativamente, el huésped puede ser considerado como inmunológicamente eficiente, por ser capaz de controlar en parte la potencialidad biológica de las células tumorales circulantes (simulando la acción frente a bacterias o virus) [72]. Existen modelos experimentales que han reconocido, por medio de la inyección vascular selectiva de células cancerosas, el aislamiento de modelos celulares metastáticos limitados a un órgano. Otros experimentos han demostrado tropismos específicos de órgano [70]. En base a la determinación de los patrones de metástasis y/ o recurrencia se han comenzado a definir perfiles genéticos de algunos cánceres [73]. Estas observaciones fundamentan la hipótesis que indica un sustrato de heterogeneidad celular y atributos biológicos en el proceso evolutivo de metastatización y recurrencia, incluyendo fenómenos de recurrencia (órgano-específicos) y ausencia de re-metastatización.

Los marcadores moleculares para la detección de metástasis ocultas son utilizados en diversos escenarios clínicos. Están ampliamente acreditados por la

practica clínica en coriocarcinomas (HCG), cánceres de testículo (HCG, LDH, AFP) cáncer de próstata (PSA), cáncer de páncreas (CA19-9) y el cáncer ovárico (CA125), entre otros.

Varios de estos cánceres pueden ser eficazmente controlados con tratamientos oportunos. El ascenso del PSA post-prostatectomía puede ser un indicador de recurrencia. La radioterapia externa puede disminuir el nivel de PSA a niveles imperceptibles. El dilema en el cáncer de próstata, sin embargo, es la predicción del órgano metastático. El PSA no permite identificar con certeza si la recurrencia es local o a sistémica, aunque generalmente anide en el compartimento de médula ósea de hueso esquelético. Su detección en el hueso, requiere el crecimiento significativo, seguido de reacción lítica o blástica en la estructura ósea. Actualmente se está evaluando la viabilidad de incorporar marcadores moleculares al sistema TNM, con el objetivo de afinar la predictibilidad de la estimación pronóstica [3].

La proyección de los radiotrazadores de productos farmacéuticos, antígenos específicos, y anticuerpos monoclonales usando la tomografía computarizada por emisión de fotón único (SPECT) y la tecnología PET, son estrategias en desarrollo para impulsar fórmulas de bio-estadificación que orienten una práctica clínica oncológica adaptada a la heterogeneidad evolutiva reconocible actualmente en los modelos de cáncer oligo-metastático y oligo-recurrente.

La identificación de patrones moleculares permitirá racionalizar y personalizar los esfuerzos terapéuticos en los pacientes portadores de enfermedad oligometástasica y/ o oligo-recurrente.

4.4.3. DETECCIÓN Y ESTRATEGIAS DE DIAGNÓSTICO.

La exactitud de las imágenes de exploración modernas [(tomografía axial computarizada (TAC) y resonancia nuclear magnética (RNM)] dependen de la sensibilidad y la especificidad para el correcto diagnóstico y detección. El tamaño tumoral que se considera umbral, con la tecnología actual, es de 5 mm: por debajo de este umbral es difícil distinguir entre estructuras normales y anormales. Si se considera una metástasis biológicamente como un esferoide, un racimo de células de 3 mm de diámetro debe inducir su propia neo-vasculatura tumoral para crecer o evolucionará a necrosis [74].

La comisión americana contra el cáncer ha definido las micrometástasis ganglionares como depósitos tumorales de entre 0.2 mm y 2.0 mm de tamaño [3]. Habitualmente, la metástasis clínicamente detectable es diagnosticada cuando presenta un diámetro de 1.0 o más cm. y se considera en esta etapa como un diagnóstico relativamente precoz. Esta es una asunción poco acertada porque biológicamente un nódulo de 1.0 cm puede contener 10^9 células y necesita haber realizado más de 20 duplicaciones para haber alcanzar este tamaño [75]. En el escenario clínico real, pueden existir múltiples micrometástasis de un tamaño menor al umbral necesario para la detección. Asumiendo la analogía de los ganglios linfáticos que el manual AJCC define como la micrometástasis nodal como los racimos de celulares de un tamaño < 0.2 mm, impone que para su detección se realicen microsecciones y técnicas de inmunohistoquímica especiales, no incorporadas aun a la practica clínica salvo por excepción en modelos singulares (cáncer de mama precoz). La imagen de alta resolución actualmente se considera a niveles menores a 0.1 mm o 100 μm en el nivel celular y subcelular. El TAC de alta resolución y la microscopía con RNM en el nivel de los 100 um requiere de radio-marcadores. La mayoría de las sondas son ligandos de receptores o proteínas [76].

Clínicamente, el elemento más validado es el 18 flourodesoxiglucosa (FDG) para la utilización de la tomografía por emisión de positrones (PET). En la práctica clínica moderna, con el movimiento de los órganos y la dimensionalidad corporal, el PET requiere que los tumores tengan de 10 a 15 mm de diámetro para poder detectarlos con fiabilidad [77]. El centro de atención actual en la detección de microfocos de cáncer se relaciona con el empleo de marcadores moleculares como sustitutos de funciones bioquímicas de tales microdepósitos. El empleo de marcadores serológicos comenzó en coriocarcinomas (HCG) y cánceres testiculares (HCG, LDH, AFP) y su presencia post-tratamiento, indicaba la confirmación molecular de micrometástasis viables. La microcuantificación y la microvisualización de cáncer oculto metastático apareció con la introducción del radioyodo (con el objetivo de detectar y localizar las micrometástasis de cáncer de tiroides con exploraciones de cuerpo totales) [70]. Las indicaciones basadas en la mejor evidencia disponible para el estudio corporal con PET/CT han aumentado significativamente, actualmente es una prueba extensamente utilizada en la práctica clínica [78]. El PET/ TAC se ha convertido en la tecnología de elección para el tamizaje de metástasis. El desarrollo de nuevos radiotrazadores específicos para cada patrón de oligo-recurrencia, optimizará la imagen anatómica en cuanto rentabilidad diagnostica en términos de sensibilidad, especificidad, y exactitud. Una ilustración de su contribución actual es confirmada por la sensibilidad que exhibe en detectar ganglios mediastínicos metabólicamente metastáticos en pacientes con cáncer pulmonar (91% 18FDG-PET vs 64% TAC) [78], con una sensibilidad y la especificidad del 98 % y 94 %, respectivamente. Para la evaluación hepática, el PET-FDG es más exacto en indicar la recurrencia o metástasis que el CT (la v del 92 % el 78 % y el 80 %, respectivamente) [79]. El

PET presenta una sensibilidad aproximada entre el 80 y 95 %, una especificidad entre 75 y 90% y una exactitud entre el 80 y 90 % para una variedad de subtipos histológicos tumorales [80]. Es apropiado concluir que existe progreso en la capacidad de diagnosticar metástasis ocultas de pequeño tamaño umbral. A medida que el tamaño de las lesiones detectadas disminuya, la fiabilidad en asignar un criterio estricto de oligo-recurrencia se incrementará. La eficiencia clínica de este progreso necesita de evaluaciones medico-económicas sobre vigilancia activa en pacientes de alto riesgo de recidiva oncológica, valor de su detección temprana y coste-eficiencia de un tratamiento de rescate eficaz.

5. Conclusiones.

5. CONCLUSIONES.

1. El rescate multimodal intensivo, en los modelos clínico-patológicos de oligo-recurrencia loco-regional evaluados, reconoce que la integración de un componente de radioterapia externa con fotones promueve resultados de control oncológico a largo plazo significativamente superiores a los conseguidos exclusivamente con cirugía y radioterapia intraoperatoria.

2. Los pacientes con resecciones R0 y fragmentación tumoral experimentan el mayor beneficio de la combinación trimodal. No obstante, en pacientes con resecciones R1 en el modelo de cáncer oligo-recurrente de origen ginecológico se identifica un efecto de compensación de adversidad pronóstica en el contexto de cirugía de máximo esfuerzo y máxima intensidad radioterápica integral.

3. El abordaje multidisciplinar del cáncer oligo-recurrente con cirugía, radioterapia intraoperatoria y externa con fotones, es una estrategia de tratamiento factible, con una tolerancia aceptable y un índice de cumplimiento terapéutico superior al 90%.

4. La terapia sistémica adyuvante no modifica la evolución oncológica de los pacientes oligo-recurrentes en los modelos clínico-terapéuticos y períodos de tiempo evaluados. Sin embargo, las metástasis sistémicas continúan siendo el patrón dominante de progresión y el mayor reto terapéutico actual. El tratamiento oportuno y agresivo de la enfermedad oligo-recurrente podría facilitar y optimizar la efectividad de los tratamientos sistémicos.

5. El cáncer oligo-recurrente, en los modelos emergentes analizados, es una nueva categoría de enfermedad oncológica curable. Existen supervivientes a largo plazo en todos los subgrupos terapéuticos y categorías de riesgo pronóstico evaluados.

6. La evidencia clínica de supervivientes a largo plazo señala la necesidad de impulsar programas de desarrollo e innovación radio-quirúrgica con prospección de la intensificación sistémica, la investigación loco-regional de sub-volúmenes de riesgo local aumentado y la minimización de secuelas crónicas que comprometan la calidad de vida de los pacientes.

6. Bibliografía.

6. BIBLIOGRAFÍA.

[1]. Halsted WS. The results of radical operations for the cure of carcinoma of the breast. Ann Surg. 1907; 46: 1–19.

[2]. Gospodarowicz M, Benedet L, Hutter RV, et al. History and international developments in cancer staging. Cancer Prevent Control. 1998; 2: 262–8.

[3]. Greene FL, Page DL, Fleming ID, et al. editor. AJCC cancer staging manual. 6th ed. New York (NY): Springer, 2002.

[4]. Burke HB, Henson DE. Criteria for prognostic factors and for an enhanced prognostic system. Cancer. 1993; 72: 3131–5.

[5]. Committees and Task Forces of the American Joint Committee for Cancer Staging and End Results Reporting. Classification and staging of cancer by site: a preliminary handbook. Chicago (IL): American Joint Committee on Cancer, 1976.

[6]. Hellman, S. & Weichselbaum, R. R. Oligometastases. J Clin Oncol. 1995 ;13: 8-10.

[7]. Weichselbaum RR, Hellman S. Oligometastases revisited. Nat Rev Clin Oncol. 2011; 8: 378-82.

[8]. Niibe Y, Kazumoto T, Toita T, et al. Frequency and characteristics of isolated para-aortic lymph node recurrence in patients with uterine cervical carcinoma in Japan: a multi-institutional study. Gynecol Oncol. 2006; 103: 435–8.

[9]. Niibe Y, Kenjo M, Kazumoto T, et al. Multi-institutional study of radiation therapy for isolated para-aortic lymph node recurrence in uterine cervical carcinoma: 84 subjects of a population of more than 5000. Int J Radiat Oncol Biol Phys. 2006; 66: 1366–9.

[10]. Niibe Y, Kuranami M, Matsunaga K, et al. Value of high-dose radiation therapy

for isolated osseous metastasis in breast cancer in terms of oligo-recurrence. Anticancer Res; 2008; 28: 3929–31.

[11]. Niibe Y, Hayakawa K. Oligometastases and Oligo-recurrence: The New Era of Cancer Therapy. Jpn J Clin Oncol. 2010; 40: 107–111.

[12]. Hughes KS, Simon R, Songhorabodi S, et al. Resection of the liver for colorectal carcinoma metastases: a multi-institutional study of patterns of recurrence. Surgery. 1986; 100: 278–284.

[13]. Nordlinger B, Guiguet M, Vaillant JC, et al. Surgical resection of colorectal carcinoma metastases to the liver. A prognostic scoring system to improve case selection, based on 1568 patients. Association Française de Chirurgie. Cancer. 1996; 77: 1254–1262.

[14]. Klein J, Dawson LA. Hepatocellular carcinoma radiation therapy: review of evidence and future opportunities. Int J Radiat Oncol Biol Phys. 2013; 87: 22-32.

[15]. Høyer M, Swaminath A, Bydder S, et al. Radiotherapy for liver metastases: a review of evidence. Int J Radiat Oncol Biol Phys. 2012; 82: 1047-57.

[16]. No authots listed. Long-term results of lung metastasectomy: prognostic analyses based on 5206 cases. The International Registry of Lung Metastases. J Thorac Cardiovasc Surg. 1997; 113: 37–49.

[17]. Salama JK, Chmura SJ, Mehta N, et al. An initial report of a radiation dose-escalation trial in patients with one to five sites of metastatic disease. Clin. Cancer Res. 2008; 14: 5255–5259.

[18]. Rusthoven KE, Kavanagh BD, Burri SH, et al. Multi-institutional phase I/II trial of stereotactic body radiation therapy for lung metastases. J Clin Oncol. 2008; 27: 1579–1584.

[19]. Milano MT, Katz AW, Zhang H, et al. Oligometastases treated with stereotactic body radiotherapy: long-term follow-up of prospective study. Int J Radiat Oncol Biol Phys. 2012; 83: 878-86.

[20]. Sole CV, Lopez Guerra JL, Matute R, et al. Stereotactic ablative radiotherapy delivered by image-guided helical tomotherapy for extracranial oligometastases. Clin Transl Oncol. 2013; 15: 484-91.

[21]. Strong VE, DÁngelica M, Tang L, et al. Laparoscopic adrenalectomy for isolated adrenal metastasis. Ann Surg Oncol. 2007; 14: 3392–3400.

[22]. Shiue K, Song A, Teh BS, et al. Stereotactic body radiation therapy for metastases to the adrenal glands. Expert Rev Anticancer Ther. 2012; 12: 1613-20.

[23]. Lopez Guerra JL, Gomez D, Zhuang Y, et al. Prognostic impact of radiation therapy to the primary tumor in patients with non-small cell lung cancer and oligometastasis at diagnosis. Int J Radiat Oncol Biol Phys. 2012; 84: 61-67.

[24]. Paget S. The distribution of secondary growths in cancer of the breast. The Lancet. 1889; 133: 571–573.

[25]. Chambers AF, Groom AC, MacDonald IC. Dissemination and growth of cancer cells in metastatic sites. Nature Reviews Cancer. 2002; 2: 563–572.

[26]. Fidler IJ. The pathogenesis of cancer metastasis: the “seed and soil” hypothesis revisited. Nature Reviews Cancer. 2003; 3: 453–458.

[27]. Ribatti D, Mangialardi G, Vacca A. Stephen Paget and the “seed and soil” theory of metastatic dissemination. Clinical and Experimental Medicine. 2006; 6: 145–149.

[28]. Langley RR, Fidler IJ. The seed and soil hypothesis revisited-the role of tumor-stroma interactions in metastasis to different organs. International Journal of Cancer. 2011; 128: 2527–2535.

[29]. Gore EM, Bae K, Wong SJ, et al. Phase III comparison of prophylactic cranial irradiation versus observation in patients with locally advanced non-small-cell lung cancer: primary analysis of radiation therapy oncology group study RTOG 0214. J Clin Oncol. 2011; 29: 272-8.

[30]. Niibe Y, Kazumoto T, Toita T, et al. Frequency and characteristics of isolated para-aortic lymph node recurrence in patients with uterine cervical carcinoma in Japan: a multiinstitutional study. Gynecol Oncol. 2006: 103; 435–438.

[31]. Gallagher DJ, Kemeny N. Metastatic colorectal cancer: from improved survival to potential cure. Oncology. 2010; 78: 237–248.

[32]. Wanebo HJ, Antoniuk P, Koness RJ, et al. Pelvic resection of recurrent rectal cancer: Technical considerations and outcomes. Dis Colon Rectum. 1999; 42: 1438-1448.

[33]. Petersen IA, Krempien R, Beauchamp C, et al. Extremity and Trunk Soft-Tissue Sarcomas. In: Gunderson LL, Willet CG, Calvo FA, Harrison LB. Intraoperative irradiation techniques and results. Current Clinical Oncology. 2nd edition. Humana Press, Springer New York Heidelberg. 2011: 387-405.

[34]. Hockel M, Dornhofer N. Pelvic exenteration for gynaecological tumours: achievements and unanswered questions. Lancet Oncol. 2006; 7: 837–47.

[35]. Perez CA, Kuske RR, Camel HM, et al. Analysis of pelvic tumor control and impact on survival in carcinoma of the uterine cervix treated with radiation therapy alone. Int J Radiat Oncol Biol Phys. 1988; 14: 613–21.

[36]. Heald RJ, Moran BJ, Ryall RDH, et al. Rectal cancer: The Basingstoke experience of total mesorectal excision, 1978-1997. Arch Surg. 1998; 133: 894-899.

[37]. Sauer R, Liersch T, Merkel S, et al. Preoperative versus postoperative

chemoradiotherapy for locally advanced rectal cancer: Results of the German CAO/ARO/AIO-94 randomized phase III trial after a median follow-up of 11 years. J Clin Oncol. 2012; 30: 1926-1933.

[38]. van Gijn W, Marijnen CA, Nagtegaal ID, et al. Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer: 12-year follow-up of the multicentre, randomised controlled TME trial. Lancet Oncol 2011; 12: 575-582.

[39]. Haas RL, Delaney TF, O'Sullivan B. Radiotherapy for management of extremity soft tissue sarcomas: why, when, and where? Int J Radiat Oncol Biol Phys. 2012; 84: 572-80.

[40]. Chemoradiotherapy for Cervical Cancer Meta-analysis Collaboration (CCCMAC). Reducing uncertainties about the effects of chemoradiotherapy for cervical cancer: individual patient data meta-analysis. Cochrane Database Syst Rev. 2010; 20: CD008285.

[41]. Hahnloser D, Nelson H, Gunderson LL, et al. Curative potential of multimodality therapy for locally recurrent rectal cancer. Ann Surg. 2003; 237: 502-508.

[42]. Dresen RC, Gosens MJ, Martijn H, et al. Radical resection after IORTcontaining multimodality treatment is the most important determinant for outcome in patients treated for locally recurrent rectal cancer. Ann Surg Oncol. 2008; 15: 1937-1947.

[43]. Wells BJ, Stotland P, Ko MA, et al. Results of an aggressive approach to resection of locally recurrent rectal cancer. Ann Surg Oncol. 2007; 14: 390-395.

[44]. Martínez-Monge R, Jurado M, Aristu JJ, et al. Intraoperative electron beam radiotherapy during radical surgery for locally advanced and recurrent cervical

cancer. Gynecol Oncol. 2001; 82: 538–43.

[45]. del Carmen MG, Eisner B, Willet CG, et al. Intraoperative radiation therapy in the management of gynecologic and genitourinary malignancies. Surg Oncol Clin N Am. 2003; 12: 1031–42.

[46]. Mahé MA, Gérard JP, Dubois JB, et al. Intraoperative radiation therapy in recurrent carcinoma of the uterine cervix: report of the French intraoperative group on 70 patients. Int J Radiat Oncol Biol Phys. 1996; 34: 21–6.

[47]. Hicks ML, Piver MS, Mas E, et al. Intraoperative orthovoltage radiation therapy in the treatment of recurrent gynecologic malignancies. Am J Clin Oncol. 1993; 16: 497–500.

[48]. Tran PT, Su Z, Hara W, et al. Long-term survivors using intraoperative radiotherapy for recurrent gynecologic malignancies. Int J Radiat Oncol Biol Phys. 2007; 69: 504–11.

[49]. Petersen IA, Haddock MG, Donohue JH, et al. Use of intraoperative electron beam radiotherapy in the management of retroperitoneal soft tissue sarcomas. Int J Radiat Oncol Biol Phys. 2002; 52: 469–475.

[50]. Krempien R, Roeder F, Oertel S, et al. Intraoperative electron beam therapy for primary and recurrent retroperitoneal soft-tissue sarcoma. Int J Radiat Oncol Biol Phys. 2006; 65: 773–779.

[51]. Tran PT, Hara W, Su Z, et al. Intraoperative radiation therapy for locally advanced and recurrent soft-tissue sarcomas in adults. Int J Radiation Oncology Biol Phys. 2008; 72: 1146–1153.

[52]. Kusters M, Dresen RC, Martijn H, et al. Radicality of resection and survival after multimodality treatment is influenced by subsite of locally recurrent rectal cancer. Int J Radiat Oncol Biol Phys. 2009; 75: 1444-1449.

[53] Haddock MG, Martinez-Monge R, Petersen IA, et al. Locally advanced primary and recurrent gynecological malignancies: EBRT with or without IOERT or HDR-IORT. In: Gunderson LL, Willett CG, Calvo FA, Harrison LB, editors. Intraoperative irradiation. Techniques and results. 2nd ed. New York: Humana Press, Springer; 2011.

[54]. LeVay J, O'Sullivan B, Catton C, et al. Outcome and prognostic factors in soft tissue sarcoma in the adult. Int J Radiat Oncol Biol Phys. 1993; 27: 1091-9.

[55]. Delaney TF, Kepka L, Goldberg SI, et al. Radiation therapy for control of soft tissue sarcomas resected with positive margins. Int J Radiat Oncol Biol Phys. 2007; 67: 1460-9.

[56]. Zagars GK, Ballo MT, Pisters PW, et al. Prognostic factors for patients with localized soft-tissue sarcoma treated with conservation surgery and radiation therapy: an analysis of 1225 patients. Cancer. 2003; 97: 2530-43.

[57]. Haddock MG, Miller RC, Nelson H, et al. Combined modality therapy including intraoperative electron irradiation for locally recurrent colorectal cancer. Int J Radiat Oncol Biol Phys. 2011; 79: 143-150.

[58]. Aubey JJ, McCreath W, Chi DS, et al. Outcomes of patients with recurrent gynecological malignancies treated with radical surgical resection and high-dose rate intraoperative radiotherapy (HDR-IORT). The 35th Annual SGO Meeting in San Diego, CA; 2004.

[59]. Braendengen M, Tveit KM, Berglund A, et al. Randomized phase III study comparing preoperative radiotherapy with chemoradiotherapy in nonresectable rectal cancer. J Clin Oncol. 2008; 26: 3687-3694.

[60]. Gunderson LL, Ashman JB, Haddock MG, et al. Integration of radiation oncology with surgery as combined-modality treatment. Surg Oncol Clin N Am. 2013; 22: 405-32.

[61]. Azinovic I, Calvo FA, Puebla F, et al. Long-term normal tissue effects of intraoperative electron radiation therapy (IOERT): Late sequelae, tumor recurrence, and second malignancies. Int J Radiat Oncol Biol Phys. 2001; 49: 597-604.

[62]. Calvo FA, González ME, González-San Segundo C, et al. Surgery and intraoperative electron radiotherapy in recurrent or metastatic oligotopic extrapelvic cancer: Long-term outcome. Eur J Surg Oncol. 2012; 38: 955-61.

[63]. Valentini V, Morganti A, Gambacorta MA, et al. Preoperative hyperfractionated chemoradiation for locally recurrent rectal cancer in patients previously irradiated to the pelvis: A multicentric phase II study. Int J Radiat Oncol Biol Phys. 2006; 64: 1129-1139.

[64]. Pacelli F, Tortorelli A, Rosa F, et al. Locally recurrent rectal cancer: prognostic factors and long-term outcomes of multimodal therapy. Ann Surg Oncol. 2010; 17: 152–162.

[65]. Haddock MG, Martinez-Monge R, Petersen IA, et al. Locally advanced primary and recurrent gynecological malignancies: EBRT with or without IOERT or HDR-IORT. In: Gunderson LL, Willett CG, Calvo FA, Harrison LB, editors. Intraoperative irradiation. Techniques and results. 2nd ed. Springer New York: Humana Press; 2011.

[66]. Dowdy SC, Mariani A, Cliby WA, et al. Radical pelvic resection and intraoperative radiation therapy for recurrent endometrial cancer: Technique and analysis of outcomes. Gynecol Oncol. 2006; 101: 280–286.

[67]. Barney BM, Petersen IA, Dowdy SC. et al. Intraoperative Electron Beam Radiation Therapy (IOERT) in the Management of Locally Advanced or Recurrent Cervical Cancer. Radiat Oncol. 2013; 8: 80. [Epub ahead of print]

[68]. Oertel S, Treiber M, Zahlten-Hinguranage A, et al. Intraoperative electron boost radiation followed by moderate doses of external beam radiotherapy in limb-sparing treatment of patients with extremity soft-tissue sarcoma. Int J Radiat Oncol Biol Phys. 2006; 64: 1416-23.

[69]. Azinovic I, Martinez Monge R, Javier Aristu J, et al. Intraoperative radiotherapy electron boost followed by moderate doses of external beam radiotherapy in resected soft-tissue sarcoma of the extremities. Radiother Oncol. 2003; 67: 331–337.

[70]. Rubin P, Brasacchio R, Katz A. Solitary metastases: illusion versus reality. Semin Radiat Oncol. 2006; 16: 120-30.

[71]. Tannock IF, Hill RP (eds). The Basic Science of Oncology (ed 3). New York, NY, McGraw-Hill, 1998.

[72]. Williams JP, Lord E, Order SE. Basic concepts of tumor immunology and principles of immunotherapy, in Rubin P (ed): Clinical Oncology, A Multidisciplinary Approach for Physicians and Students (ed 8). Philadelphia, PA, Saunders, 2005: 185-198.

[73]. Tamoto E, Tada M, Murakawa K, et al. Gene-expression profile changes correlated with tumor progression and lymph node metastasis in esophageal cancer. Clin Cancer Res 2004; 10: 3629-3638.

[74]. Sutherland RM, McCredie JA, Irch WR. Growth of multiple spheroids in tissue culture as a model of nodule carcinomas. J Nat Cancer Inst. 1971; 46: 113-120.

[75]. Collins VP, Loeffler RK, Tiery H. Observations on growth rates of human tumors. Am J Roentgenol Ther Nucl Med. 1956; 76: 988-1000.

[76]. Sullivan DC, Tatum JL. Imaging at the molecular levels, in Bragg DG, Rubin P, Hricak H (eds): Oncologic Imaging (ed 2). Philadelphia, PA, Saunders, 2002: 69-78.

[77]. Kim EE, Lee M-C, Inoue T, et al. Clinical PET, Principles and Applications. New York, NY, Springer-Verlag New York Inc, 2004.

[78]. Kim EE, Wong FCL. Thoracic cancer, in Kim EE, Lee M-C, Inoue T, et al (eds): Clinical PET, Principles and Applications. New York, NY, Springer-Verlag New York Inc, 2004; 262-282

[79]. Kim BT, Kim EE. Hepatobiliary tumors, in Kim EE, Lee M-C, Inoue T, et al: Clinical PET, Principles and Applications. New York, NY, Springer- Verlag New York Inc, 2004; 314-324.

[80]. Juweid ME, Cheson BD. Positron-emission tomography and assessment of cancer therapy. N Engl J Med. 2006; 354: 496-507.

7. Anexos.

7.1. RESUMEN EN CASTELLANO

7.1.1. INTRODUCCIÓN.

Los avances en el tratamiento de los pacientes con sarcoma de tejidos blandos, cáncer rectal y ginecológico en los últimos 15 años, han reducido significativamente el riesgo de recidiva local; sin embargo, el abordaje oncológico de la oligo-recurrencia loco-regional es un desafío pendiente en el siglo 21 [1]. La categoría de oligo-recurrencia loco-regional es un espectro amplio de situaciones clínico-patológicas. En numerosos artículos se ha comunicado que algunos pacientes pueden beneficiarse de la terapia local intensiva [2]. La práctica clínica ha evolucionado desde la no intervención y/o (quimio) radioterapia paliativa hacia enfoques de rescate multimodales combinados [2]. Diversos estudios han descrito que la radicalidad de la resección es el predictor más importante de supervivencia [3].

No obstante lograr una resección con márgenes negativos (sin afectación neoplásica) es a menudo difícil debido a la proximidad o invasión de estructuras adyacentes no resecables. En este contexto, enfoques multimodales, incluyendo terapias locales complementarias y de efecto oncológico aditivo se han explorado en un intento de promover la optimización del control local y de la supervivencia [4]. Dada la baja incidencia de oligo-recurrencia loco- regional, existe una carencia de ensayos aleatorios que evalúen diferentes esquemas de tratamiento [5]. En este contexto hemos investigado factores de riesgo y resultados a largo plazo en grupos de pacientes pertenecientes a modelos clínico-patológicos con oligo - recurrencia loco- regional de tumores primarios rectales, ginecológicos y de sarcoma de tejidos (análisis individual de cada grupo) susceptibles de rescate con resección quirúrgica seguida de radioterapia intraoperatoria radioterapia con electrones

(RIO) en las zonas de alto riesgo (después de la resección y antes de la reconstrucción) con o sin radioterapia externa (RTE) .

7.1.2. MATERIALES Y MÉTODOS.

7.1.2.1. CRITERIOS DE SELECCIÓN DE PACIENTES.

Este estudio fue aprobado por los comités institucionales del Hospital General Universitario Gregorio Marañón (oligo - recurrencia de sarcoma de partes blandas, rectales y ginecológicos), Hospital Universitario Ramón y Cajal (oligo-recurrencia de sarcoma de partes blandas) y la Clínica Universitaria de Navarra (oligo-recurrencia de sarcoma de partes blandas). A los sujetos con enfermedad loco-regionalmente oligo-recurrente con confirmación patológica (sarcoma de tejidos blandos, adenocarcinoma rectal y carcinomas epidermoides y adenocarcinomas de origen ginecológico) se les ofreció participar en un protocolo coordinado de tratamiento que consistía en re-estadificación extensiva, cirugía de rescate local de máximo esfuerzo y RIO sobre la zona en riesgo de enfermedad residual en el lecho quirúrgico. El abordaje quirúrgico, el uso de RTE pre- o postoperatoria y el uso de quimioterapia adyuvante se discutió de forma individualizada. En la evaluación multidisciplinar se consideró la categoría de enfermedad oncológica original, las características iniciales de tratamiento, la localización de la oligo-recurrencia, la resecabilidad tumoral y el estado clínico de los pacientes. Se revisaron retrospectivamente los registros hospitalarios (entre junio de 1986 y abril de 2012) de 60 pacientes tratados por oligo-recurrencia loco-regional de cáncer de recto , 103 pacientes tratados por oligo-recurrencia local de tumores primarios de sarcoma de tejidos blandos (extremidades, 43 % ; centrales o de tronco, 24 % ; retroperitoneo, 33%) y 61 pacientes tratados por oligo-recurrencia loco-regional

de tumores originalmente ginecológicos (cérvix, 52%; endometrial, 30 %; ovario, 15 %; vagina, 3 %).

7.1.2.2. DETALLES DEL TRATAMIENTO.

El tratamiento con RTE, quimioterapia concomitante, adyuvante y RIO se basó en normas descritas anteriormente [6].

2.2.1. Se planificó radioterapia convencional hasta el año 1992. Se planificó radioterapia conformada tridimensional (desde 1993), teniendo en cuenta las dosis administradas a los tejidos normales incluidos en el volumen de la radioterapia originaria para el tumor primario dependiendo de las incidencias y contribuciones de los campos de irradiación. Sin embargo, no se especificaron limitaciones de dosis-volumen en el protocolo de re-tratamiento. La mediana de dosis total fue de 45 Gy (rango, 45 a 50,4 Gy)/ 1,8 Gy por fracción /5 días por semana para los pacientes no irradiados previamente y 30,6 Gy (rango de 21,6 a 30,6 Gy)/ 1,8 Gy por fracción/ 5 días por semana para los pacientes previamente irradiados (re-irradiados para rescate).

2.2.2. La quimioterapia concomitante consistió en una fluoropirimidina oral (Tegafur), 1,2 g por día para los tumores de recto y cisplatino por vía intravenosa en bolo (75 mg/m2/d1 y d5 cada 4 semanas por 2 veces) para tumores de cuello uterino. Los pacientes tenían 4 semanas de descanso después de la cirugía y posteriormente podían recibir QT adyuvante.

2.2.3. Después de la cirugía y antes de la reconstrucción anatómica, de 10 a 15 Gy (mediana, 12,5 Gy) fueron administrados en una sola fracción de irradiación a una región anatómica con 1 o 2 campos, utilizando una mediana de energía de 12 MeV (rango, 6-18 MeV). El estado de los márgenes se evaluó intraoperatoriamente mediante secciones patológicas con espécimen tisular en congelación. Los

aplicadores circulares biselados (0º a 45 º) de metacrilato (rango de tamaño, 5 a 15 cm) se ajustaron para colimar la superficie del volumen blanco de tratamiento en la anatomía post-quirúrgica, lo que permitió una mejor adaptación y uniformidad de distribución dosimétrica.

7.1.2.3. SEGUIMIENTO Y EVALUACIÓN DE LA TOXICIDAD.

Todos los pacientes fueron programados para seguimiento en un protocolo multi-institucional común cada 3 meses después de finalizar el tratamiento para los 3 primeros años y cada 6 meses a partir de los 3 años. Los pacientes fueron re-estadificados 4 semanas después del término de la RTE y cada 6 meses con TC. La evaluación de las complicaciones quirúrgicas se realizó de acuerdo a la clasificación Clavien-Dindo. La toxicidad aguda y se evaluó de acuerdo con la escala del Grupo de Oncología Radioterápica/ Organización Europea para la Investigación y Tratamiento del Cáncer (RTOG/ EORTC).

7.1.2.4. ANÁLISIS ESTADÍSTICO.

Los datos obtenidos fueron analizados mediante el software estadístico SPSS (versión 19.0). El objetivo principal del análisis fue el control loco-regional (CLR). Los objetivos secundarios fueron la supervivencia global (SG) y la supervivencia libre de enfermedad (SLE). El método de Kaplan - Meier se utilizó para estimar las probabilidades de CLR, SG y SLE. Las asociaciones potenciales de eventos fueron evaluadas en mediante análisis univariante y multivariante utilizando el modelo de riesgos proporcionales de Cox [test valor p <0.05 (2 caras)]. El ajuste del modelo se realizó para los factores significativos en el análisis univariante [test valor p <0.1 (2 caras)].

7.1.3. RESULTADOS.

7.1.3.1. OLIGO-RECURRENCIA LOCO- REGIONAL DE TUMOR PRIMARIO RECTAL.

El tiempo medio de seguimiento para toda la cohorte de pacientes fue de 36 meses (rango, 2-189 meses). La SG de la población de estudio a 1, 3 y 5 años fue de 78 %, 53 % y 43 %, respectivamente. En el análisis multivariable, la resección R1 y la ausencia de fragmentación tumoral mostraron una asociación significativa en relación a la SG. EL CLR a 1, 3 y 5 años fue de 86 %, 52 % y 44 %, respectivamente. En el análisis multivariante la resección R1, el no recibir RTE en el tratamiento de la RLR, la presencia de ganglios linfáticos metastáticos en el espécimen operatorio y la ausencia de fragmentación tumoral retuvieron una asociación estadísticamente significativa. La SLE a 1, 3 y 5 años fue de 81 %, 46 % y 37 %, respectivamente. El análisis multivariante mostró que la ausencia de fragmentación tumoral se asocia con un menor riesgo de metástasis. Las causas de toxicidad aguda y crónica se estimaron como multifactoriales. En total, 25 pacientes (42 %) presentaron toxicidad aguda grado ≥ 3, y 12 pacientes (20%) experimentaron toxicidad crónica grado ≥ 3.

7.1.3.2. CÁNCER OLIGO-RECURRENTE GINECOLÓGICO.

La mediana de tiempo de seguimiento para la cohorte completa de pacientes fue de 46 meses (rango, 3-169). La supervivencia global de la población de estudio a 5 y 10 años fue de 42 y 16%, respectivamente. En el análisis multivariante se observa que el intervalo de tiempo desde el diagnóstico del tumor primario a la RLR < 24 meses y no recibir RTE en el momento de RLR se asociaron significativamente con la SG.

El CLR a 5 y 10 años fue de 58 %, en ambos casos. El análisis multivariante de riesgos proporcionales de Cox mostró que el intervalo de tiempo (< 24 meses) desde el diagnóstico del tumor primario a la RLR, el no recibir RTE en el momento de la RLR y la ausencia de fragmentación tumoral mostraron una asociación

significativa con el CLR. La SLE a 5 y 10 años fue de 46 y 35 %, respectivamente. El análisis multivariado evidenció que el intervalo (< 24 meses) desde el diagnóstico del tumor primario a la RLR y no el recibir RTE en el tratamiento de la RLR, retuvieron importancia en cuanto al control loco-regional. Un total de 14 pacientes (39 %) desarrollaron toxicidad aguda grado ≥ 3 y 8 pacientes (23 %) desarrollaron toxicidad tardía grado ≥ 3.

7.1.3.3. CÁNCER OLIGO-RECURRENTE DE SARCOMA DE PARTES BLANDAS.

La mediana de seguimiento para el grupo completo de pacientes fue de 57 meses (rango, 2-311). El control local de la población de estudio a los 5 y 10 años fue de 60% y 58%. En el análisis multivariable el no recibir RTE sobre la RLR y el presentar márgenes R1 se asociaron con una mayor probabilidad de RLR. La SLE a 5 y 10 años fue de 43 % y 33%. Tras el ajuste por otras variables, en el análisis multivariante se observó que el intervalo (<24 meses) entre el diagnóstico del tumor primario y la recidiva local, el grado histológico alto (G3) y el estado del margen (R1), mantuvieron una asociación significativa con la SLE. La supervivencia global a los 5 y 10 años fue de 52% y 33%. El análisis multivariante mostró que sólo el estado del margen (R1) y el tiempo (<24 meses) desde el diagnóstico del tumor primario a la recidiva local se asociaron significativamente con la SG. En total, 16 pacientes (16%) presentaron toxicidad aguda y 13 pacientes (13%) desarrollaron toxicidad crónica grado ≥ 3.

7.1.4. DISCUSIÓN.

El concepto de oligometástasis implica una carga tumoral restringida y un patrón evolutivo indolente, por lo que se ha propuesto a este grupo de pacientes como candidatos a estrategias de tratamiento intensificado mediante la combinación de cirugía, radioterapia y quimioterapia [1]. La categoría de oligo-recurrencia

locoregional es heterogénea e incluye varios subtipos de enfermedad oncológica [2]. Sin embargo, los pacientes con oligo-recurrencia loco–regional presentan una carga tumoral limitada y se ha propuesto como un criterio común para la optimización de la estrategia de terapéutica de rescate [2]. Se ha observado y documentado que algunos pacientes en esta situación particular, podrían beneficiarse de una terapia local intensificada [6].

Reconocemos varias limitaciones en el presente estudio. La muestra clínica y patológica analizada es heterogénea y el período evaluado prolongado, habiendo sido tratados en más de 16 años los tumores de recto, 18 años los tumores ginecológicos y 26 años los sarcomas de partes blandas (se asume que la cirugía y oncología se han actualizado y mejorado su eficiencia clínica). Aunque se observó una asociación entre el tratamiento con radioterapia externa y el control local, la presencia de un sesgo de selección de los pacientes referidos a una dosis más alta no se puede descartar. Los pacientes que no recibieron RTE tenían mayores reservas relacionadas con la toxicidad del re-tratamiento o existía una mayor incertidumbre clínica relacionada con la eficacia del tratamiento. Además, es muy difícil evaluar la contribución específica del componente de RIO, debido a que en el presente análisis no se compararon grupos con o sin RIO. Sin embargo los elementos metodológicos del componente de RIO han sido meticulosamente analizados.

7.1.4.1. CÁNCER OLIGO-RECURRENTE RECTAL.

Nuestros resultados relevantes se pueden resumir de la siguiente manera. En primer lugar, encontramos que la resección quirúrgica extendida compensa ciertas características adversas asociadas a la RLR. En segundo lugar, se encontró que no agregar RTE a la cirugía y RIO para el rescate de pacientes con oligo-recurrencia

loco- regional de tumor primario rectal se asoció significativamente con un aumento del riesgo de RLR. Además, el valor del uso de RTE mantiene significación estadística cuando los pacientes con resección R0 y con fragmentación tumoral se analizaron por separado. Por último, se encontró que los pacientes sin fragmentación del tumor tenían resultados clínicos más favorables a largo plazo.

Aunque el número de estudios que evalúan cirugía, RIO y RTE en pacientes con oligo-recurrencia loco-regional de tumor primario rectal es limitado, los principales resultados del presente análisis (CLR a 5 años de 44% y SG a 43%) son comparables con los descritos en la literatura (CLR a 5 años 30%-75% y SG a 5 años 20%-50%) [7]. Haddock et al. [7] comunicó la mayor experiencia institucional de tratamiento de rescate con RIO para pacientes con oligo-recurrencia loco-regional de primario colorrectal (n=607). Aunque no se proporcionan datos detallados sobre la región anatómica de recurrencia susceptible de rescate quirúrgico, el resultado fue más favorable para las recurrencias de primarios de colon (vs. recto) (supervivencia a 5 años de 34% vs. 28 %, p=0.07). Kusters et al. [3] analizó 170 pacientes sometidos a tratamiento multimodal con RTE preoperatoria con quimioterapia sensibilizante, cirugía y RIO. Los peores resultados se observaron en los pacientes con recurrencias presacras [28% resecciones completas y 19% de supervivencia a 5 años (p = 0.03)]. Alternativamente, se observaron los resultados más favorables en los pacientes con recurrencias anastomóticas [77% de resecciones R0 y 60% de supervivencia a los 5 años (p=0.04)]. En un análisis anterior Calvo et al. [4] evaluó la factibilidad y los resultados a largo plazo de pacientes con oligo-recurrencia extrapélvica (n=28) tratados con cirugía y RIO. Con una mediana de tiempo de seguimiento de 39 meses, observó que los pacientes con un compromiso mayor al 50% de los

fragmentos tumorales presentaron mayor riesgo de RLR (38% vs. 9%, p=0.02). En el análisis actual, el no presentar fragmentación tumoral se asocia a mejores resultados de control oncológico a largo plazo.

Varios estudios han comunicado que la re-irradiación pélvica con una dosis total de RTE moderada (<35 Gy) es tolerable, con tasas moderadas de toxicidad tardía y que su efecto promueve el control local [8]. En el presente análisis, los pacientes re-irradiados (n = 7) no presentaron peores resultados de supervivencia, probablemente porque 5 de 7 pacientes tuvieron resecciones R0, por lo que fue difícil detectar una ventaja ante los pacientes sin re-irradiación (n = 21). Valentini et al. [8] ha identificado que en pacientes con oligo-recurrencia loco-regional de tumor primario rectal que habían recibido previamente radioterapia externa pélvica la supervivencia global alcanzó a 5 años el 39%, a pesar de que el 87.4% de los pacientes presentaban extensión a pared lateral (resecciones R0, 35%; SG a 5 años de 64%).

En el presente análisis observamos que los pacientes que recibieron RTE pre-operatoria obtienen los mejores resultados oncológicos [9]. Pacelli et al. [9] informó en un análisis de pacientes con resecciones potencialmente curativas (R0 a R1) que la quimio-radioterapia preoperatoria mejoraba la SG a 5 años (44,6 vs 25,8 %, p = 0,012). La secuencia óptima de tratamientos multimodales y la contribución de un componente de RTE y RIO en este complejo escenario clínico es controvertida y merece nuevos análisis basados en el rescate adaptado al riesgo individual.

En lo que se refiere a la toxicidad relacionada con el tratamiento, la tolerancia parece aceptable, las tasas de complicaciones post-quirúrgicas sugieren que un

enfoque multidisciplinar experto, con un componente de cirugía extendida es factible y sin efectos secundarios prohibitivos a largo plazo.

7.1.4.2. CÁNCER OLIGO-RECURRENTE GINECOLÓGICO.

Nuestros resultados más relevantes se pueden resumir de la siguiente manera. En primer lugar, se observó que no añadir RTE a la cirugía y RIO se asoció a un incremento en el riesgo de re-recurrencia local, metástasis y muerte. En segundo lugar, los pacientes con oligo-recurrencias para-aórticas presentaron un mayor riesgo de metástasis en comparación con los pacientes con oligo-recurrencias pélvicas. En tercer lugar, hemos observado que los pacientes con un intervalo de tiempo de entre el diagnóstico del tumor primario y la RLR < 24 meses, presentaron un mayor riesgo de re-recidiva local y muerte. Por último, los pacientes sin fragmentación tumoral presentaron un menor riesgo de re-recurrencia local.

Varias instituciones expertas en RIO han analizado cohortes mixtas con amplios criterios de inclusión y resultados comparables al presente análisis. Nuestra evaluación no seleccionó pacientes por el origen del tumor primario, ni modalidades de tratamiento inicialmente radicales, ni por volumen o extensión de la recurrencia tumoral y, asimismo, se incluyeron pacientes con oligo-recurrencia pélvica y para-aórtica.

La discriminación entre los tumores localmente avanzados y loco-regionalmente oligo-recurrentes es importante porque la supervivencia (SG a 10 años, 14 vs. 67 %, p < 0,001) y el control local (control en campo de RIO, 47 vs. 93 %, p < 0,001) de los pacientes tratados con tumores primarios es superior [10].

Con frecuencia se ha informado una asociación entre la realización de una resección quirúrgica completa (R0/R1 resección) y un control local y

supervivencia superiores [11]. En un análisis de la Clínica Mayo [11] se analizaron 148 pacientes (84 % oligo-recurrentes) con tumores ginecológicos tratados con resección quirúrgica máxima más RIO (76 % RTE). El CLR y la SG a 5 años fueron de 60 % y 27 %. Los pacientes con resecciones R2 tuvieron una supervivencia significativamente menor que los pacientes con resecciones R0/R1 (SG a 5 años, 13 vs. 31 %, p = 0.01).

La tasa de metástasis a distancia a 5 años fue inferior en los pacientes con resecciones R0/R1 (49%) respecto a R2 (58 %), aunque el CLR a 5 años fue de 74 % para los pacientes con resecciones R2 frente a 58% para los pacientes con resecciones R0/R1. El elevado control local observado en pacientes R2 puede ser explicado por la mayor tasa de metástasis a distancia y la muerte antes de que la recidiva local se manifestara clínica o radiológicamente. Aubey et al. [12] analizó 56 pacientes tratados con resección radical seguida de RIO con braquiterapia de alta tasa de dosis. Con una mediana de seguimiento de 11,4 meses, la tasa de supervivencia a los 2 años para los pacientes con resecciones R2 fue de 20 % frente al 60% para aquellos con resecciones R0/R1 ($p < 0,01$). Mahe et al. [13] ha comunicado en un análisis multi-institucional de centros sanitarios de origen Francés, que no observó ninguna diferencia en la tasa de metástasis a distancia al estratificar por márgenes de resección. Sin embargo, dado que la frecuencia de CLR en el grupo con márgenes R2 fue de 16%, es probable que muchos de estos pacientes fallecieran de la progresión de la enfermedad local antes que las metástasis a distancia fueran detectables.

En el presente grupo de estudio el uso de una estrategia multimodal integrando un componente de RIO ha modificado aparentemente la planificación y extensión de la resección quirúrgica (ningún paciente tenía enfermedad residual

macroscópica). En lo que se refiere a la extensión de la resección quirúrgica (R0 vs R1) no evidenciamos diferencias en CLR ni SG. En la experiencia de la Clínica Mayo [11], se comunicó una supervivencia inferior para los pacientes con un intervalo libre de enfermedad ≤ 2 años en comparación con aquellos con un intervalo > 2 años (SG a 5 años, 14 vs 35 %, p=0.002). Nuestra observación de que los pacientes con un intervalo <24 meses tuvieron resultados globales más comprometidos que los pacientes con un intervalo ≥ 24 meses es consistente con los hallazgos mencionados anteriormente.

La contribución clínica de incluir un componente de RTE en un tratamiento de rescate multimodal es incierta. En pacientes previamente irradiados (se asume que tienen una biología adquirida de radioresistencia) se han comunicado resultados adversos y más comprometidos; sin embargo, esta observación no ha sido confirmada en la serie actual, ni en otra experiencia publicada previamente [11]. La serie de la Clínica Mayo de 25 pacientes con cáncer de endometrio oligo-recurrente [14], mostró que el empleo de RTE se asoció con una mejor supervivencia (p = 0.019). En la serie de la Clínica Mayo de 89 pacientes con cáncer de cuello uterino [oligo-recurrentes (83 %) y primarios localmente avanzados (17 %)] tratados con RIO después de la resección quirúrgica (69 % recibió RTE) [15], en el análisis multivariante la exenteración pélvica y la RTE se asociaron con una control local superior. En consonancia, con este hallazgo encontramos que los pacientes sin tratamiento de RTE tuvieron resultados globales inferiores al compararlos con los que recibieron RTE. Como datos singulares del presente análisis, los pacientes con fragmentación tumoral y resecciones R0 tratados con RTE tenían mejor control local que los que no recibieron RTE. En el contexto de estas aportaciones parciales, permanece pendiente de nuevos estudios la

definición de la secuencia óptima de tratamiento junto con la contribución individual de los componentes de RTE y/o RIO.

Se ha informado de que los pacientes con oligo-recurrencia exclusiva en la región para-aórtica pueden lograr un excelente control local y supervivencia después de terapia de rescate [2]. En el análisis actual, aunque los pacientes con oligo-recurrencia para-aórtica aislada presentaron un control local y supervivencia comparables con los pacientes con oligo-recurrencia pélvica, observamos una mayor incidencia de re-metastatización en general lo que sugiere un potencial de migración celular superior (exhibido al poderse considerar a este sub-grupo como oligo-recurrencia regional en sí mismo).

Los resultados de toxicidad relacionada con el tratamiento, la tolerancia y las tasas de complicaciones post-quirúrgicas sugieren que un enfoque multimodal que incluye un componente de RIO y RTE es factible con riesgos tolerables y sin efectos prohibitivos a largo plazo.

7.1.4.3. CÁNCER OLIGO-RECURRENTE DE SARCOMA DE PARTES BLANDAS.

Hasta donde llega nuestro conocimiento actualizado, este es el primer estudio que se centra en los resultados a largo plazo en pacientes con oligo-recurrencia local de sarcoma de partes blandas tratados con un componente de RIO, después de la resección quirúrgica asociado o no a RTE. Nuestros hallazgos más relevantes se pueden resumir de la siguiente manera. En primer lugar, se observó que la combinación de RTE, resección quirúrgica y RIO se asoció significativamente con una disminución en la probabilidad de RLR y recaída dentro del campo de RIO. En segundo lugar, se encontró que los pacientes con un intervalo de tiempo < 24 meses entre el diagnóstico del tumor primario y la oligo-recurrencia local presentan una mayor probabilidad de metástasis y muerte. Finalmente, los

pacientes con márgenes microscópicos positivos presentan peores resultados globales.

Varias instituciones expertas en RIO, que evalúan en sus programas pacientes con amplios criterios de inclusión (cohortes mixtas de pacientes con primarios localmente avanzados y oligo-recurrencias locales; sarcomas de extremidades, tronco o centrales y retroperitoneales), han informado resultados comparables a los descritos en el presente análisis. La singularidad del presente análisis es la inclusión selectiva de pacientes con oligo-recurrencias locales. La selección no se basó en la localización original del sarcoma, el volumen de la recurrencia o las modalidades de tratamiento iniciales. En todos los casos se confirmaron márgenes cercanos (< 1 cm) o positivos (R1), lo que implica una resección técnicamente difícil y un pronóstico oncológico adverso [16]. La discriminación entre un sarcoma primario localmente avanzado y un sarcoma localmente oligo-recurrente es importante, ya que los pacientes oligo-recurrentes se asocian con resultados clínicos más adversos [17]. Varios grupos han desarrollado con éxito estrategias de tratamiento combinado (RIO y resección quirúrgica) en cohortes mixtas de pacientes (control local a 5 años, 60-80 %) [17]. Aunque está ampliamente aceptado que la calidad del margen quirúrgico es de suma importancia en la promoción del control local, las características específicas que constituye un margen quirúrgico adecuado no está totalmente plenamente definido. Diversos grupos expertos insisten consistentemente en que los márgenes quirúrgicos positivos son un factor pronóstico de adversidad [18, 19]. Oertel et al. [18] comunicó un control local y SG a 5 años de 78% y 77 %, en la mayor experiencia institucional de RIO en pacientes con sarcoma de partes blandas publicada a la fecha (n = 153, 32% oligo-recurrentes). Se observó que el control local fue más

favorable para los pacientes con resecciones completas (CL a 5 años 85% vs. 60%, p=0.03). Azinovic et al. [19] analizó 45 pacientes con sarcomas de extremidades (42 % oligo-recurrentes) tratados con RTE postoperatoria y RIO. El control local a 5 años fue de 87 % y el estado del margen (márgenes negativos o cercanos vs. márgenes positivos, p=0.04) afectó significativamente el control local. En el análisis actual, la presencia de márgenes de resección microscópica positivos se asoció significativamente con resultados comprometidos a largo plazo.

El grado histológico es un factor predictivo independiente para el desarrollo de metástasis en los pacientes con sarcoma de partes blandes [17]. En el modelo de sarcoma oligo-recurrente también se confirma que el grado histológico es un factor pronóstico independiente de SLE.

Aunque el efecto de la quimioterapia adyuvante en la supervivencia no está totalmente dilucidado en pacientes con sarcoma de partes blandas [20], el patrón dominante de progresión en este grupo sigue siendo las metástasis a distancia. Es importante considerara que el potencial del tratamiento local intensificado tiene que ser evaluado en el contexto de tratamientos sistémicos concurrentes, neo-adyuvantes y adyuvantes, para mostrar mayor efectividad integral.

Azinovic et al. [18] observó que los pacientes que recibieron RTE adyuvante presentaron un mejor control local mayor que los pacientes que no recibieron RTE (85% vs. 74%). En el presente análisis, identificamos que los pacientes que no recibieron RTE no sólo presentaron un mayor riesgo de recidiva local, sino que también presentaron un mayor riesgo de recidiva dentro del campo de RIO. Aunque la mayoría de las re-recurrencias locales se presentaron dentro del campo de RIO (69%), una escalada de dosis moderada con valores superiores a 12. 5 Gy no se asociaron a un mejor control local.

El tratamiento fue bien tolerado por los pacientes. Las bajas tasas de efectos tóxicos graves sugieren que un enfoque multimodal con re-resección, RIO y RTE es factible sin efectos secundarios prohibitivos a largo plazo.

El compromiso de radicalidad quirúrgica y el riesgo asociado a la ubicación anatómica de un sarcoma oligo-recurrente se debe evaluar con esmero e individualización durante la administración de la RIO y RTE con el fin de ajustar al mínimo el volumen irradiado al riesgo post-quirúrgico. La definición de órganos de riesgo (dosis-sensibles), la disponibilidad de histogramas de dosis-volumen y las estimaciones de la distribución dosimétrica tridimensional debe contribuir a la optimización metodológica de la RIO. La pre-planificación detallada y compartida por parte del cirujano y el oncólogo radioterápico, junto con la integración multidisciplinar del radiólogo y del patólogo en el momento de la resección (intraplanificación), será decisivo para promover estrategias de escalada de dosis en el lecho tumoral (técnicas de campo dentro del campo y sub-volúmenes de sobreimpresión).

El escenario hospitalario de la RIO basa su excelencia en una actividad interdisciplinar exigente e innovadora, y en la relación multi-profesional [21-23]. El paciente con cáncer oligo-recurrente debe tener opción a ser evaluado por grupos expertos en rescate multidisciplinar intensificado.

7.1.5. CONCLUSIONES.

En conclusión, los pacientes con oligo-recurrencia loco- regional pertenecientes a diferentes modelos clínico-patológicos que recibieron RTE y RIO lograron mejores resultados oncológicos a largo plazo sin un aumento en la toxicidad. El dato más original evaluado respecto al riesgo de recidiva local es la fragmentación tumoral. Las resecciones R0 experimentaron el mayor beneficio con el tratamiento con RTE.

No obstante, un cierto nivel de adversidad pronóstico (resecciones R1) puede ser compensada en un contexto de máxima intensidad terapéutica. Por último, la terapia sistémica adyuvante no contribuyó de forma relevante en el abordaje radical de estos pacientes en los períodos de tiempo evaluados. Sin embargo, debido a que las metástasis sistémicas son un patrón de progresión frecuente en pacientes oligo-recurrentes, el desarrollo de terapias sistémicas más efectivas jugará un papel decisivo en el progreso terapéutico de estos pacientes. La terapia sistémica neo-adyuvante, concomitante y adyuvante en diferentes combinaciones con terapia local intensificada tiene un fundamento conceptual que debe ser probado en el escenario metodológico de un ensayo clínico. El futuro de la investigación clínica debe centrarse en la intensificación loco-regional en sub-volúmenes de riesgo, en la promoción del resultado anatómico-funcional favorable y en la minimización de secuelas que comprometan la calidad de vida de los pacientes.

7.1.6. BIBLIOGRAFÍA.

[1]. Weichselbaum RR, Hellman S. Oligometastases revisited. Nat Rev Clin Oncol. 2011; 8: 378-82.

[2]. Niibe Y, Hayakawa K. Oligometastases and Oligo-recurrence: The New Era of Cancer Therapy. Jpn J Clin Oncol. 2010; 40: 107–111.

[3]. Kusters M, Dresen RC, Martijn H, et al. Radicality of resection and survival after multimodality treatment is influenced by subsite of locally recurrent rectal cancer. Int J Radiat Oncol Biol Phys. 2009; 75: 1444-1449.

[4]. Calvo FA, González ME, González-San Segundo C, et al. Surgery and intraoperative electron radiotherapy in recurrent or metastatic oligotopic extrapelvic cancer: Long-term outcome Eur J Surg Oncol. 2012; 38: 955-61.

[5]. Braendengen M, Tveit KM, Berglund A, et al. Randomized phase III study comparing preoperative radiotherapy with chemoradiotherapy in nonresectable rectal cancer. J Clin Oncol. 2008; 26: 3687-3694.

[6]. Gunderson LL, Willett CG, Calvo FA, et al. editors. Intraoperative irradiation. Techniques and results. 2nd ed. Springer New York: Humana Press; 2011.

[7]. Haddock MG, Miller RC, Nelson H, et al. Combined modality therapy including intraoperative electron irradiation for locally recurrent colorectal cancer. Int J Radiat Oncol Biol Phys. 2011; 79: 143–50.

[8]. Valentini V, Morganti A, Gambacorta MA, et al. Preoperative hyperfractionated chemoradiation for locally recurrent rectal cancer in patients previously irradiated to the pelvis: A multicentric phase II study. Int J Radiat Oncol Biol Phys. 2006; 64: 1129-1139.

[9]. Pacelli F, Tortorelli A, Rosa F, et al. Locally recurrent rectal cancer: prognostic

factors and long-term outcomes of multimodal therapy. Ann Surg Oncol. 2010; 17: 152–162.

[10]. Martínez-Monge R, Jurado M, Aristu JJ, et al. Intraoperative electron beam radiotherapy during radical surgery for locally advanced and recurrent cervical cancer. Gynecol Oncol. 2001; 82: 538-43.

[11]. Haddock MG, Martinez-Monge R, Petersen IA, et al. Locally advanced primary and recurrent gynecological malignancies: EBRT with or without IOERT or HDR-IORT. In: Gunderson LL, Willett CG, Calvo FA, Harrison LB, editors. Intraoperative irradiation. Techniques and results. 2nd ed. New York: Humana Press, Springer; 2011.

[12]. Aubey JJ, McCreath W, Chi DS, et al. Outcomes of patients with recurrent gynecological malignancies treated with with radical surgical resection and high-dose rate intraoperative radiotherapy (HDR-IORT). The 35th Annual SGO meeting in San Diego, CA; 2004.

[13]. Mahe MA, Gerard JP, Dubois JB, et al. Intraoperative radiation therapy in recurrent carcinoma of the uterine cervix: Report of the French intraoperative group on 70 patients. Int J Radiat Oncol Biol Phys. 1996; 34: 21–26.

[14]. Dowdy SC, Mariani A, Cliby WA, et al. Radical pelvic resection and intraoperative radiation therapy for recurrent endometrial cancer: Technique and analysis of outcomes. Gynecol Oncol. 2006; 101: 280–286.

[15]. Barney BM, Petersen IA, Dowdy SC, et al. Intraoperative Electron Beam Radiation Therapy (IOERT) in the Management of Locally Advanced or Recurrent Cervical Cancer. Radiat Oncol. 2013; 8: 80. [Epub ahead of print]

[16]. LeVay J, O'Sullivan B, Catton C, et al. Outcome and prognostic factors in soft tissue sarcoma in the adult. Int J Radiat Oncol Biol Phys. 1993; 27: 1091-9.

[17]. Petersen IA, Krempien R, Beauchamp C, et al. Extremity and Trunk Soft-Tissue Sarcomas. In: Gunderson LL, Willet CG, Calvo FA, Harrison LB. Intraoperative irradiation techniques and results. Current Clinical Oncology. 2nd edition. Humana Press, Springer New York Heidelberg. 2011: 387-405.

[18]. Oertel S, Treiber M, Zahlten-Hinguranage A, et al. Intraoperative electron boost radiation followed by moderate doses of external beam radiotherapy in limb-sparing treatment of patients with extremity soft-tissue sarcoma. Int J Radiat Oncol Biol Phys. 2006; 64: 1416-23.

[19]. Azinovic I, Martinez Monge R, Aristu JJ, et al. Intraoperative radiotherapy electron boost followed by moderate doses of external beam radiotherapy in resected soft-tissue sarcoma of the extremities. Radiother Oncol. 2003; 67: 331-337.

[20]. Pervaiz N, Colterjohn N, Farrokhyar F, et al. A systematic meta-analysis of randomized controlled trials of adjuvant chemotherapy for localized resectable soft tissue sarcoma. Cancer. 2008; 113: 573-81.

[21]. Krengli M, Calvo FA, Sedlmayer F, et al. Clinical and technical characteristics of intraoperative radiotherapy. Analysis of the ISIORT-Europe database. Strahlenther Onkol. 2013; 189: 729-37.

[22]. Gunderson LL, Ashman JB, Haddock MG, et al. Integration of radiation oncology with surgery as combined-modality treatment. Surg Oncol Clin N Am. 2013; 22: 405-32.

[23]. Debenham BJ, Hu KS, Harrison LB. Present status and future directions of intraoperative radiotherapy. Lancet Oncol. 2013; 14: 457-64.

7.2. RESUMEN EN INGLÉS

7.2.1. INTRODUCTION

Although the improvements achieved in the treatment of soft-tissue sarcoma, rectal and gynecological cancer over the past 15 years, have reduced the risk of local recurrence after potentially curative resection, management of loco-regional oligorecurrence remains a major oncologic challenge in the 21st century [1]. Loco-regional oligo-recurrence is a broad disease category, and it has been reported that some patients may benefit from intensive local therapy [2]. Clinical practice has shifted from non-intervention or palliative (chemo) radiation to more intensive multimodal approaches combined with intended radical surgery [2]. Several studies have reported that radicality of the resection is the most significant predictor of improved survival [3]. Nonetheless achievement of a complete negative resection margin is often questionable because of close proximity or proven invasion into adjacent unresectable structures. Therefore, multimodal approaches including additional local therapies might be implemented to further improve patient outcomes and optimize local control and survival [4]. Given the rarity of loco-regional oligo-recurrence, randomized trials evaluating various treatment regimens are difficult to conduct, and to our knowledge few studies of this nature have been published to date [5]. In this context, we investigated outcomes and novel risk factors for a group of patients with locoregional oligo-recurrence from soft-tissue sarcoma, rectal and gynecologic primary tumors treated with surgical resection followed by intraoperative radiation therapy electron-beam radiation therapy (IOERT) in high-risk areas (after resection and before reconstruction) with and without external beam radiation therapy (EBRT).

7.2.2 METHODS AND MATERIALS.

7.2.2.1. PATIENT SELECTION CRITERIA.

This study was approved by the institutional review board of Gregorio Marañon General University Hospital (loco-regional oligo-recurrence of soft-tissue sarcoma, rectal and gynecological tumors), Ramón y Cajal University Hospital (loco-regional oligo-recurrence of soft-tissue sarcoma) and Navarra University Clinic (loco-regional oligo-recurrence of soft-tissue sarcoma). Subjects with pathologically confirmed loco-regional oligo-recurrent disease (soft-tissue sarcoma, rectal and gynecologic primary tumors) were offered to participate in a developmental treatment protocol that consisted of rescue surgery and IOERT to the tumor bed area at risk for residual disease. Consideration for surgical approach, pre- or postoperative EBRT, and adjuvant chemotherapy (CT) was discussed on an individualized basis. For multimodal recommendation, Tumor Boards considered initial treatment characteristics, location, tumor resectability, and clinical status of patients. Prospectively collected hospital records of 60 patients treated for loco-regional oligo-recurrence of rectal primary tumors, 103 patients treated for local oligo-recurrence of soft tissue sarcoma primary tumors (extremity, 43%; trunk wall, 24%; retroperitoneum, 33%) and 61 patients treated for loco-regional oligo-recurrence of gynecologic primary tumors (uterine cervix, 52%; endometrial, 30%; ovarian, 15%; vagina, 3%) between June 1986 and April 2012 were retrospectively reviewed.

7.2.2.2. TREATMENT DETAILS.

Details of EBRT and of concomitant and adjuvant CT followed standards previously described [6].

2.2.1. EBRT was delivered with megavoltage equipment (6-15 MV). Conformal 3-dimensional radiation therapy was planned; fields were arranged taking into

account doses delivered to normal tissues during radiation therapy for primary tumor. However, no specific dose-volume constraints were indicated by the treatment protocol. A total median dose of 45 Gy (range, 45-50.4 Gy), 1.8 Gy/5 days/week for patients not previously irradiated (n=22) and 30.6 Gy (range, 21.6-30.6 Gy), 1.8 Gy/5 days/week for patients previously irradiated (n=6) was prescribed to the isodose line, which covered the planning target volume (PTV).

2.2.2. Chemotherapy concomitant schedule consisted of oral fluoropirimidine (Tegafur), 1.2 g/day in rectal tumors and bolus intravenous cisplatin (75 mg/m2/d1 and d5, Qw4 x 2) in gynecological tumors. Patients had a 4-week rest after surgery and then could receive additional adjuvant CT.

2.2.3. IOERT was performed in nondedicated linear accelerators with outpatient radiation therapy activity in the three institutions. After surgery and before any anatomic reconstruction required, 10 to 15 Gy (median, 12.5 Gy) were delivered in a single fraction to a 1-field or 2-field PTV (tumor bed and/ or residual post-resected areas), using a median energy of 12 MeV (range, 6-18 MeV). Intraoperative margin status was assessed using frozen pathologic sections. Bevelled (0º to 45º) Lucite circular applicators (size range, 5-15 cm) were adjusted to collimate the target surface air gap, allowing dosimetric adaptation and uniform dose distribution. CT-guided treatment has been available since 2008.

7.2.2.3. FOLLOW-UP AND TOXICITY EVALUATION.

All patients were scheduled to be followed up according to a common protocol every 3 months after treatment completion for the initial 3 years and every 6 months for 3 additional years thereafter. Patients were restaged 4 weeks after RT (before surgery) and routinely every 6 months with CT scan. Assessment of surgical complications was done according to the Clavien-Dindo classification.

Acute and late toxicities were evaluated according to Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer score.

7.2.2.4. STATISTICAL ANALYSIS.

The data collected were analyzed by SPSS (version 19.0) statistical software. The primary endpoint of the analysis was locoregional control (LRC). Secondary endpoints were OS, disease-free survival (DFS). The Kaplan-Meier method was used to estimate the probabilities of LRC, OS and DFS. Potential associations were assessed in univariate and multivariate analyses by the Cox proportional hazards model (2-sided P test 0.05). Adjustment was performed for factors significant on univariate analysis (2-sided P test <0.10).

7.2.3. RESULTS.

7.2.3.1. OLIGO-RECURRENT RECTAL CANCER.

The median follow-up time for the entire cohort of patients was 36 months (range, 2-189 months). The OS for the study population at 1, 3, and 5 years was 78%, 53%, and 43%, respectively. On multivariate Cox proportional hazard analyses R1 resection and no tumor fragmentation showed a significant association with OS. The 1-year, 3-year, and 5-year rates of LRC were 86%, 52%, and 44%, respectively. We found on multivariate analysis that R1 resection, EBRT integrated at the time of LRR, nonmetastatic lymph nodes, and no tumor fragmentation retained significance. DFS at 1, 3, and 5 years was 81%, 46%, and 37%, respectively. Multivariate analyses showed that no tumor fragmentation was associated with a lower risk of DFS. Causes of acute and chronic toxicity were estimated as multifactorial. Overall, 25 patients (42%) had grade ≥ 3 acute toxicity and 12 patients (20%) experienced grade ≥ 3 chronic toxicity.

7.2.3.2. OLIGO-RECURRENT GYNECOLOGICAL CANCER.

Median follow-up time for the entire cohort of patients was 46 months (range, 3–169). Median follow-up time for surviving patients was 67 months (range, 5–169). Overall survival for the study population at 5-, and 10-years was 42 and 16%, respectively. We found on multivariate analysis that time interval from primary tumor diagnosis to LR < 24 months and not receiving EBRT at the time of LRR retained significance. The 5- and 10-year rates of LRC were 58 and 58%, respectively. Multivariate Cox proportional hazard analyses showed that time interval from primary diagnosis to LR < 24 months, not receiving EBRT to the LR and no tumor fragmentation showed a significant association with LRC. DFS at 5- and 10-years was 46 and 35%, respectively. On multivariate analyses primary tumor diagnosis to LR < 24 months and not receiving EBRT to the LR, retained significance in regard to DFS . Overall 14 patients (39%) had grade ≥ 3 acute toxicity and 8 patients (23%) developed chronic toxicity grade ≥ 3.

7.2.3.3. OLIGO-RECURRENT SOFT TISSUE SARCOMA.

Median follow-up time for all patients was 57 months (range, 2-311). Local control for the study population at 5 and 10 years was 60% and 58%. Multivariate Cox proportional hazard analyses showed that no EBRT to the LR and R1 margin status were associated with an increased chance of LRR. DFS at 5 and 10 years was 43% and 33%. After adjustment for other covariates, primary tumor diagnosis to local relapse < 24 months (p=0.006), high histological grade (p=0.04), and incomplete margin status (p=0.03) retained a significant association with DFS. Overall survival at 5 and 10 years was 52% and 33%. Multivariate analysis showed that only R1 margin status (p=0.02) and primary tumor diagnosis to local relapse < 24 months (p=0.006) were significantly associated with OS. Overall, 16 patients (16%) had grade ≥ 3 acute toxicity and 13 patients (13%) developed chronic

toxicity grade ≥ 3.

7.2.4. DISCUSSION.

Oligometastasis implies a restricted locoregional tumor burden and has been proposed as a status candidate for intense treatment strategies combining surgery, radiotherapy and chemotherapy [1]. Loco-regional oligo-recurrence is a broad disease category comprising several types of patient and tumor profiles [2]. Oligorecurrence involves a restricted locoregional tumor burden and has been proposed as a common criterion for treatment strategy optimization [2]. It has been constantly reported that some patients in this particular scenario could potentially benefit from intensified local therapy [6].

We acknowledge several limitations of our study. The patient population was heterogeneous, having been treated over 16 years for rectal tumors, 18 years for gynecological tumors and 26 years for soft tissue sarcomas (receiving multimodal treatment that evolved with the oncological progress over time). Although we did observe an association between EBRT treatment and LRC after adjustment for several potential confounding factors, the presence of a selection bias for patients referred for radiation therapy to a higher integral dose cannot be completely dismissed. We certainly acknowledge that patients that did not consent EBRT had greater concerns related to re-treatment toxicity or issues related to treatment efficacy (in particular, re-irradiation). A rigorous and systematic method of follow-up, including imaging, would be optimal to evaluate patterns of failure after radiation therapy. Finally, it is very difficult to assess the specific contribution of the IOERT treatment component, because this analysis did not compared treatment with or without intraoperative electron irradiation.

7.2.4.1. OLIGO-RECURRENT RECTAL CANCER.

Our relevant findings can be summarized as follows. First, we found that extended surgical resection compensates for adverse LR related features. Second, we found that not adding EBRT to surgery and IOERT in patients with LRRC was significantly associated with a decreased risk of LRC. Interestingly, this maintained significance when patients with radical resection and tumor fragmentation were analyzed separately. Finally, we found that patients with no tumor fragmentation had a decreased probability of LR, DF, and overall mortality and that patients undergoing R1 resections had lower rates of LRC and OS. Although the number of studies assessing patients with LRRC undergoing rescue operation with surgery, intraoperative radiotherapy, and EBRT is limited, the most relevant results reported in the present article (5-year LRC 44% and OS 43%) are comparable with those reported in the literature (5-year LRC 30%-75% and OS 20%-50%) [7]. Haddock et al [7]. reported the largest institutional expert experience with IOERT for the rescue of recurrent colorectal cancer (n=607). Although detailed data on the site of recurrence and rescue are not provided, the outcome was more favourable for recurrence in the colon than in the rectum (5-year survival 34% vs 28%, p=0.07). Kusters et al. [3] analyzed 170 patients with LRRC who underwent multimodality treatment with preoperative CRT, elective radical surgery, and IOERT. The worst outcomes were seen in presacral recurrences: 28% complete resections and 19% 5-year survival (p=0.03). The most favourable outcomes were observed for anastomotic LRRC, with 77% R0 resections and 60% 5-year survival (p=0.04). Consistently, we also found that patients with nonradical resections had worse overall outcomes than did patients with radical resections. In a previous report [4] we evaluated the feasibility and long-term outcome of surgery combined with IOERT in patients with recurrent oligotopic extrapelvic cancer (n=28). With a

median follow-up time of 39 months, we found that LR was significantly affected by microscopic cancer in more than 50% of specimen fragments (38% vs 9%, p=0.02). In the current analysis, no tumor fragmentation was associated with an improved chance of LRC, DMFS, and OS. To this end, several studies have shown that pelvic reirradiation with a low total dose of EBRT is acceptably tolerated, with moderate rates of late toxicity, and may help promote pelvic control [8]. In our report, patients being reirradiated (n=7) did not have worse survival outcomes, probably because 5 of 7 patients had R0 resections, thus making it difficult to detect an advantage among patients without reirradiation (n=21). Valentini et al. [8] reported in patients with LRRC who had previously received pelvic EBRT a 5-year overall survival of 39%, despite 87.4% of patients having sidewall involvement disease (35% R0 resections; 64% were alive at 5 years). Our finding that preoperative EBRT to LRRC patients was associated with improved outcomes is consistent with prior studies [9]. Pacelli et al. [9] reported in a subset analysis of LRRC patients with potentially curative resection (R0 to R1) that preoperative chemoradiation therapy improved 5-year OS (44.6 vs 25.8%, p=0.012). However, data regarding the optimal treatment sequence and the contribution of an EBRT component to this clinical scenario remain to be elucidated. In regard to treatment-related toxicity, the acceptable tolerance and rate of postsurgical complications suggest that a multimodality approach with an extended surgical component for LRRC is feasible with tolerable risks and without prohibitive long-term side effects.

7.2.4.2. GYNECOLOGICAL OLIGO-RECURRENT CANCER.

Our most relevant findings can be summarized as follows. First, we observed that not adding EBRT to surgery and IOERT to patients with ORGC was significantly

associated with an increased probability of LRR, overall metastases and death. Second, patients with paraaortic LR had an increased risk of overall metastases when compared to patients with pelvic LR. Third, we found that patients with a time interval < 24 months between primary tumor diagnosis and LR had an increased probability of LR and death. Finally, patients without tumor fragmentation had a decreased probability of LRR.

Several IORT-expert institutions have analysed mixed cohorts with broad inclusion criteria and reported results comparable to this retrospective single centre study. The present analysis had no selection as to primary site, modalities of initial treatment, volume of tumor recurrence and included patients with pelvic and paraaortic ORGC. Discrimination between ORGC and primary advanced tumors is important because survival (10-year OS 14 vs. 67%; $p<0.001$) and local control (10-year IOERT in field control 47 vs. 93%; $p<0.001$) of patients treated for primary advanced disease has been reported to be superior [10]. Improved survival and LRC has been frequently reported to be associated to the achievement of a gross total resection (R0/R1 resection) prior to IORT [11]. In an updated Mayo Clinic data [11] reported by Haddock et al. 148 patients (84% ORCG) with gynecological tumors were treated with maximal surgical resection plus IOERT (76% EBRT). The 5-year LRC and OS was 60% and 27% for the total group. Patients with an R2 resection had a significantly lower survival than patients with R0/R1 resection (5-year OS 13 vs. 31%; $p=0.01$). The distant metastases rate was decreased in patients with R0/R1 vs. R2 resection (5-year 49 vs. 58%), but LRC at 5-years was 74% for patients with R2 resection versus 58% for patients with R0/R1 resection. The high LRC in R2 patients may be explained to the increased rate of distant metastases and subsequent death before local relapse was clinically

evident. Aubey et al. [12] reported 56 patients with ORGC that were treated with radical resection followed by HDR-IORT. With a median follow-up of 11.4 months, 2-year survival rate for patients with R2 resections was 20% compared to 60% for those with R0/ R1 resections ($p<0.01$). A French multi-institutional analysis reported by Mahe et al. [13] observed no difference in the distant metastatic rate. However, because LRC rate in the R2 group was 16% it is likely that many of these patients died of uncontrolled local disease progression prior to distant metastases manifestation. In the current series the use of an IOERT containing multimodality strategy has impacted the extent of surgical resection (no patient had gross residual disease); in regard to the extent of surgical resection (R0 vs. R1) we found no difference in LRC or OS. In the mentioned Mayo Clinic experience [11], a worse survival was reported for patients with a disease-free interval (DFI) ≤ 2- years compared to those with a DFI > 2-years (5-year OS 14 vs. 35%; $p=0.002$). Our observation that patients with a DFI < 24 months had worse overall outcomes than patients with a DFI ≥ 24 months is consistent with previously reported findings. The clinical significance of including an EBRT-component in a multimodality IORTcontaining treatment for ORGC is uncertain. Previously irradiated patients (with assumed radioresistant biology) have been associated to adverse and worse overall results, but this observation has not been confirmed in the current series or other expert institutional analysis [11]. A combinatorial dose escalation strategy combining EBRT and IORT has not been consistently associated with improved outcomes. The Mayo Clinic series of 25 recurrent endometrial cancer patients [14] showed that EBRT was associated with improved survival ($p=0.019$). In the Mayo Clinic series of 89 patients with cervical cancer [locally recurrent (83%) or primary advanced (17%)] treated with IOERT following surgical resection (69%

received perioperative EBRT) [15]. Pelvic exenteration and perioperative EBRT were associated with improved LRC on multivariate analysis. Consistently with this finding, we observed that patients without EBRT treatment of the LR had inferior overall outcomes than patient treated with EBRT. Even more, patients with tumor fragmentation and R0 resection treated without EBRT had worse LRC than those who did received EBRT treatment. However, the optimal treatment sequence together with the magnitude of the contribution of the EBRT and IOERT components in this clinical scenario remains to be elucidated.

It has been reported that patients with ORGC exclusively in the paraaortic region can achieve excellent LRC and survival with salvage therapy [2]. In the current analysis, although paraaortic isolated lymph node recurrence was associated with equivalent LRC and survival rates when compared to pelvic recurrence, an increased incidence of overall metastases was observed suggesting a superior migration potential.

The interpretation of treatment related toxicity, tolerance and rate of postsurgical complications suggests that a multimodality approach including an IORT component for ORGC is feasible with tolerable risks and not limited by prohibitive long-term side effects.

7.2.4.3. OLIGO-RECURRENT SOFT-TISSUE SARCOMA.

To our knowledge, this is the first study to focus on long-term outcomes in patients with LR-STS treated with IOERT, surgical resection and EBRT. Our most relevant findings can be summarized as follows. First, we observed that not combining EBRT with surgical resection and IOERT in patients with LR-STS was significantly associated with an increased probability of LR and IOERT in-field relapse. Second, we found that patients with a time interval <24 months between

primary tumor diagnosis and local relapse had an increased probability of overall metastasis and death. Finally, patients with microscopically positive margins had worse overall outcomes. Several expert IOERT institutions with broad inclusion criteria (primary advanced and locally recurrent) and mixed cohorts of extremity, trunk wall, and retroperitoneal sarcomas have reported results comparable to those reported in the present analysis. The present analysis included only patients with LR-STS. Selection was not based on primary site, volume of tumor recurrence, or modalities of initial treatment. All cases had close margins (<1 cm) or positive margins (R1), features related to difficult surgical resection and adverse prognosis [16].

Discrimination between primary advanced and LR-STS in IOERT-based studies is important, because worse overall outcomes are consistently described for LR-STS [17]. Several groups have successfully implemented and reported combined management (IORT and surgical resection) in mixed cohorts for patients with primary and LR-STS (5-year local control [60-80%]) [17].

Although it is widely accepted that the quality of the surgical margin is of paramount importance for local control, what constitutes an adequate surgical margin is not well established. Positive surgical margins have been consistently reported as an adverse prognostic factor for local control [18, 19]. Oertel et al. [18] reported high 5-year local control (78%) and OS (77%) in the largest single institution experience reported to date (n=153), in which IOERT combined with moderate doses of EBRT for the management of extremity STS (32% recurrent). Local control was more favourable for patients with a negative resection margin (5-year locoregional control 85% vs 60%, p=0.03). Azinovic et al. [19] analyzed 45 patients with extremity sarcomas (42% recurrent tumors) treated with moderate-

dose postoperative EBRT (45 to 50 Gy) and IOERT. Five-year local control was 87%, and margin status (negative or close margins vs. positive margins [p=0.04]) significantly affected local control. In the current analysis, positive microscopic resection margins were significantly associated with adverse overall outcomes in the multivariate analysis. Histological grade is an independent predictive factor for development of metastasis in most cases of adult STS [17]. Unsurprisingly, therefore, grade was also an independent prognostic feature for DFS in the present analysis. Intensified local treatment needs to be tested in the context of more efficient concurrent, neoadjuvant, and adjuvant systemic therapy. Although the effect of adjuvant chemotherapy on survival for resected STS has yet to be established [20], distant metastases remain the dominant pattern of progression for oligo-recurrent STS.

As reported by Azinovic et al. [18] patients receiving adjuvant EBRT in the current analysis had a higher local control rate than patients in whom EBRT was omitted (85% vs 74%). Even more, we observed that not receiving EBRT for the local relapse was associated with an increased likelihood of IOERT in-field relapse. Although most LR-STS tumors recurred within IOERT field (69%), in the present analysis a higher IOERT dose did not improved local control.

Treatment-related toxicity, including specific damage potentially induced by IOERT administration, was acceptably tolerated by our 103 patients. The low rate of severe toxic events suggests that a multimodality approach with re-resection and IOERT is feasible without prohibitive long-term side effects. Location-associated risk should be carefully assessed during IOERT administration in order to optimize the irradiated volume at risk. The definition of organs at risk (dose-sensitive), availability of dose-volume histograms, and estimations of 3D dose

distribution, will play a key role in optimization of IOERT. Detailed planning on the part of the surgeon and radiation oncologist, along with detailed input from the radiologist prior to surgery and from the pathologist at the time of resection, is decisive for dose-escalation strategies within the tumor bed (field-within-field technique) [21-23].

7.2.5. CONCLUSIONS.

In conclusion, we found that patients with oligo-recurrent cancer that received EBRT and IOERT were treated safely and had improved outcomes. We also found that patients with tumor fragmentation and R0 resections experienced the largest benefit with EBRT treatment. A certain level of prognostic adversity (R1 resections) might be compensated. Finally, it must be emphasized that systemic therapy should play an important role in the management of LRRC. Up-front chemotherapy followed by either switch/continuation maintenance or observation in different combinations with local therapy should be tested in the scenario of a prospective clinical trial, if possible. Future clinical research should focus on anathomo-functional outcome and quality of life.

7.2.6. BIBLIOGRAPHY.

[1]. Weichselbaum RR, Hellman S. Oligometastases revisited. Nat Rev Clin Oncol. 2011; 8:378-82.

[2]. Niibe Y, Hayakawa K. Oligometastases and Oligo-recurrence: The New Era of Cancer Therapy. Jpn J Clin Oncol. 2010; 40: 107–111.

[3]. Kusters M, Dresen RC, Martijn H, et al. Radicality of resection and survival after multimodality treatment is influenced by subsite of locally recurrent rectal cancer. Int J Radiat Oncol Biol Phys. 2009; 75: 1444-1449.

[4]. Calvo FA, González ME, González-San Segundo C, et al. Surgery and intraoperative electron radiotherapy in recurrent or metastatic oligotopic extrapelvic cancer: Long-term outcome. Eur J Surg Oncol. 2012; 38: 955-61.

[5]. Braendengen M, Tveit KM, Berglund A, et al. Randomized phase III study comparing preoperative radiotherapy with chemoradiotherapy in nonresectable rectal cancer. J Clin Oncol. 2008; 26: 3687-3694.

[6]. Gunderson LL, Willett CG, Calvo FA, Harrison LB, editors. Intraoperative irradiation. Techniques and results. 2nd ed. Springer New York: Humana Press; 2011.

[7]. Haddock MG, Miller RC, Nelson H, et al. Combined modality therapy including intraoperative electron irradiation for locally recurrent colorectal cancer. Int J Radiat Oncol Biol Phys. 2011;79:143–50.

[8]. Valentini V, Morganti A, Gambacorta MA, et al. Preoperative hyperfractionated chemoradiation for locally recurrent rectal cancer in patients previously irradiated to the pelvis: A multicentric phase II study. Int J Radiat Oncol Biol Phys. 2006; 64: 1129-1139.

[9]. Pacelli F, Tortorelli A, Rosa F, et al. Locally recurrent rectal cancer: prognostic

factors and long-term outcomes of multimodal therapy. Ann Surg Oncol. 2010; 17:152–162.

[10]. Martínez-Monge R, Jurado M, Aristu JJ et al. Intraoperative electron beam radiotherapy during radical surgery for locally advanced and recurrent cervical cancer. Gynecol Oncol. 2001; 82:538-43.

[11]. Haddock MG, Martinez-Monge R, Petersen IA, et al. Locally advanced primary and recurrent gynecological malignancies: EBRT with or without IOERT or HDR-IORT. In: Gunderson LL, Willett CG, Calvo FA, Harrison LB, editors. Intraoperative irradiation. Techniques and results. 2nd ed. New York: Humana Press, Springer; 2011.

[12]. Aubey JJ, McCreath W, Chi DS, et al. Outcomes of patients with recurrent gynecological malignancues treated with with radical surgical resection and high-dose rate intraoperative radiotherapy (HDR-IORT). The 35th Annual SGO meeting in San Diego, CA; 2004.

[13]. Mahe MA, Gerard JP, Dubois JB, et al. Intraoperative radiation therapy in recurrent carcinoma of the uterine cervix: Report of the French intraoperative group on 70 patients. Int J Radiat Oncol Biol Phys. 1996; 34:21–26.

[14]. Dowdy SC, Mariani A, Cliby WA, et al. Radical pelvic resection and intraoperative radiation therapy for recurrent endometrial cancer: Technique and analysis of outcomes. Gynecol Oncol. 2006; 101:280–286.

[15]. Barney BM, Petersen IA, Dowdy SC. et al. Intraoperative Electron Beam Radiation Therapy (IOERT) in the Management of Locally Advanced or Recurrent Cervical Cancer. Radiat Oncol. 2013; 8:80. [Epub ahead of print]

[16]. LeVay J, O'Sullivan B, Catton C, et al. Outcome and prognostic factors in soft tissue sarcoma in the adult. Int J Radiat Oncol Biol Phys. 1993; 27:1091-9.

[17]. Petersen IA, Krempien R, Beauchamp C, et al. Extremity and Trunk Soft-Tissue Sarcomas. In: Gunderson LL, Willet CG, Calvo FA, Harrison LB. Intraoperative irradiation techniques and results. Current Clinical Oncology. 2nd edition. Humana Press, Springer New York Heidelberg. 2011:387-405.

[18]. Oertel S, Treiber M, Zahlten-Hinguranage A, et al. Intraoperative electron boost radiation followed by moderate doses of external beam radiotherapy in limb-sparing treatment of patients with extremity soft-tissue sarcoma. Int J Radiat Oncol Biol Phys. 2006; 64:1416-23.

[19]. Azinovic I, Martinez Monge R, Aristu JJ, et al. Intraoperative radiotherapy electron boost followed by moderate doses of external beam radiotherapy in resected soft-tissue sarcoma of the extremities. Radiother Oncol. 2003; 67:331–337.

[20]. Pervaiz N, Colterjohn N, Farrokhyar F, et al. A systematic meta-analysis of randomized controlled trials of adjuvant chemotherapy for localized resectable soft tissue sarcoma. Cancer. 2008; 113:573-81.

[21]. Krengli M, Calvo FA, Sedlmayer F, et al. Clinical and technical characteristics of intraoperative radiotherapy. Analysis of the ISIORT-Europe database. Strahlenther Onkol. 2013; 189:729-37.

[22]. Gunderson LL, Ashman JB, Haddock MG, et al. Integration of radiation oncology with surgery as combined-modality treatment. Surg Oncol Clin N Am. 2013; 22:405-32.

[23]. Debenham BJ, Hu KS, Harrison LB. Present status and future directions of intraoperative radiotherapy. Lancet Oncol. 2013; 14:e457-64.

7.3. CONCLUSIONES EN INGLÉS.

1. In the analysed clinical - pathological models the integration of EBRT to the multimodal management of patients with loco-regional oligo-recurrence improves long-term outcomes when compared with surgery and IOERT without EBRT.

2. Patients with R0 resections and tumour fragmentation experienced the largest benefit of combined therapy. Nevertheless, we observed a compensatory effect for patients with R1 resections in the oligo-recurrent gynaecological model in the context of surgery of maximum effort and combined radiotherapy intensity.

3. A multidisciplinary approach for oligo-recurrent cancer patients with surgery, IOERT and EBRT, is a feasible treatment with acceptable acute and chronic toxicity rates.

4. Adjuvant systemic therapy does not modify the oncological outcomes in this group of patients. Nonetheless, distant metastases continues to be the dominant pattern of progression and the biggest therapeutic challenge.

5. In the emergent analyzed models, oligo-recurrence emerges as a curable oncologic disease. We observed long-term survivors in all the evalauated therapeutic subgroups and risk categories.

6. The clinical evidence of long-term survivors indicates the urgent need to promote development and innovation in surgical and radio-oncological programs. Further exploration of systemic therapy intensification, investigation of local areas at increased risk and minimization of chronic sequels that compromise the quality of life of patients is warranted.

International Journal of Radiation Oncology biology • physics

www.redjournal.org

Clinical Investigation: Gastrointestinal Cancer

Prognostic Impact of External Beam Radiation Therapy in Patients Treated With and Without Extended Surgery and Intraoperative Electrons for Locally Recurrent Rectal Cancer: 16-Year Experience in a Single Institution

Felipe A. Calvo, MD, PhD,[*,§,||] Claudio V. Sole, MD,[*,§,||,¶] Pedro Alvarez de Sierra, MD, PhD,[†,||] Marina Gómez-Espí, MD,[*,‡,§] Jose Blanco, MD,[*,§] Miguel A. Lozano, MD,[*,‡,§] Emilio del Valle, MD,[†,§] Marcos Rodriguez, MD,[†,§] Alberto Muñoz-Calero, MD,[†,§] Fernando Turégano, MD,[†,§] Rafael Herranz, MD,[*,‡,§,||] Luis Gonzalez-Bayon, MD, PhD,[†,§] and Jose Luis García-Sabrido, MD, PhD[†,§,||]

**Department of Oncology, [†]Service of General Surgery, [‡]Service of Radiation Oncology, and [§]Institute of Research Investigation, Hospital General Universitario Gregorio Marañón; and [||]School of Medicine, Complutense University, Madrid, Spain; and [¶]Service of Radiation Oncology, Instituto de Radiomedicina, Santiago, Chile*

Received Dec 17, 2012, and in revised form Feb 20, 2013. Accepted for publication Apr 4, 2013

Summary

Recognition of the high risk of local rerecurrence and death in locally recurrent rectal cancer has led to interest in the use of radical intent surgical resection, external beam radiation therapy and intraoperative electron beam radiation therapy. These mature data add further evidence that intensified radiation and surgical treatment promotes locoregional control, compensating some adverse disease features in the

Purpose: To analyze prognostic factors associated with survival in patients after intraoperative electrons containing resective surgical rescue of locally recurrent rectal cancer (LRRC).

Methods and Materials: From January 1995 to December 2011, 60 patients with LRRC underwent extended surgery (n=38: multiorgan [43%], bone [28%], soft tissue [38%]) or nonextended (n=22) surgical resection, including a component of intraoperative electron-beam radiation therapy (IOERT) to the pelvic recurrence tumor bed. Twenty-eight (47%) of these patients also received external beam radiation therapy (EBRT) (range, 30.6-50.4 Gy). Survival outcomes were estimated by the Kaplan-Meier method, and risk factors were identified by univariate and multivariate analyses.

Results: The median follow-up time was 36 months (range, 2-189 months), and the 1-year, 3-year, and 5-year rates for locoregional control (LRC) and overall survival (OS) were 86%, 52%, and 44%; and 78%, 53%, 43%, respectively. On multivariate analysis, R1 resection, EBRT at the time of pelvic rerecurrence, no tumor fragmentation, and non-lymph node metastasis retained significance with regard to LRR. R1 resection and no tumor fragmentation showed a significant association with OS after adjustment for other covariates.

Conclusions: EBRT treatment integrated for rescue, resection radicality, and not involved fragmented resection specimens are associated with improved LRC in patients with locally recurrent rectal cancer. Additionally, tumor fragmentation could be compensated by EBRT. Present results

Reprint requests to: Claudio V. Sole, MD, Hospital General Universitario Gregorio Marañon, C/ Dr Esquerdo, 46 - 28007 Madrid, Spain. Tel: (34) 91-586-85-99; E-mail: cvsole@uc.cl

Supported in part by a grant from the Health Institute of Research Carlos III, Spanish Ministry of Science and Innovation (project code PI11-02908).

Conflict of interest: none.

Int J Radiation Oncol Biol Phys, Vol. 86, No. 5, pp. 892–900, 2013
0360-3016/$ - see front matter
http://dx.doi.org/10.1016/j.ijrobp.2013.04.008

context of an advanced multimodality rescue strategy.

suggest that a significant group of patients with LRRC may benefit from EBRT treatment integrated with extended surgery and IOERT. © 2013 Elsevier Inc.

Introduction

Although the improvements achieved in the treatment of rectal cancer over the past 15 years, such as total mesorectal excision and radiation/chemoradiation therapy regimens, have reduced the risk of local recurrence after potentially curative resection, the average incidence of pelvic failure is still 5% to 15% (1-3). Locally recurrent rectal cancer (LRRC) is a broad disease category, and it has been reported that some patients may benefit from intensive local therapy (4, 5). Clinical practice has shifted from nonintervention or palliative (chemo) radiation to more intensive multimodal approaches combined with intended radical surgery (6, 7). Several studies have reported that radicality of the resection of LRRC is the most significant predictor of improved survival (8-10). Nonradical resections are associated with 5-year survival rates between 0% and 15%, whereas this rate increases to 52% after radical resections (8). Achievement of complete negative margin resection is often questionable because of close proximity or proven invasion into adjacent unresectable structures. Therefore, multimodal approaches including additional local therapies might be implemented to further improve patient outcomes and optimize local control and survival (6, 10, 11). Given the rarity of LRRC, randomized trials evaluating various treatment regimens are difficult to conduct, and to our knowledge few studies of this nature have been published to date (12). In this context, we investigated outcomes and novel risk factors for an expert single-institution group of patients with LRRC treated with extended or radical intent nonextended surgery followed by intraoperative radiation therapy electron-beam radiation therapy (IOERT) in high-risk areas (after resection and before reconstruction) with and without external beam radiation therapy (EBRT).

Methods and Materials

Patient selection criteria

This study was approved by the institutional review board and was performed in compliance with hospital ethics and clinical practice guidelines. Subjects with pathologically confirmed LRRC without extrapelvic disease were offered to participate in a developmental institutional treatment protocol that consisted of rescue surgery and IOERT to the tumor bed area at risk for residual disease. Consideration for surgical approach, perioperative EBRT, and adjuvant chemotherapy (CT) was discussed on an individualized basis. For multimodal recommendation, the Tumor Board considered initial treatment characteristics, location, tumor resectability, and clinical status of patients. Prospectively collected hospital records of 60 patients treated for LRRC between January 1995 and December 2011 were retrospectively reviewed. Patients were assessed at baseline by digital examination when possible, abdominal and pelvic computed tomography (CT) scan, pelvic magnetic resonance imaging (MRI), and chest x-ray. A classification system based on CT scan and MRI was used in the evaluation of the extent of infiltration on the pelvic sidewall and the topographic site of local recurrence (LR) (13). Five groups were defined to classify the extent of infiltration on the pelvic sidewall: F0 (n = 2, 3%), no evidence of contact with the pelvic sidewall; F1 (n = 17, 28%), extent of contact less than a quarter of the pelvic sidewall; F2 (n = 7, 12%), contact less than half the circumference; F3 (n = 16, 27%), contact more than half the circumference; F4 (n = 18, 30%), involvement of bony structures or small bowel. Topographic LR was classified into 1 of the following regions: (*1*) posterior: predominantly midline, in contact with the sacral bone (n = 32, 453%); (*2*) posterolateral: laterally located, near to or invading the piriform muscle, in contact with the sacral bone (n = 20, 33%); or (*3*) anterior-lateral: in association with anterior located organs, pelvic sidewalls, or along the iliac vessels (n = 8, 14%). Patient and treatment characteristics are listed in Table 1. Compared treatment-based cohorts of patients were well balanced between patients receiving extended surgical resection (n = 38, 63%) and nonextended surgical resection (n = 22, 37%). We found that patients in the extended surgery group had more advanced tumors with greater extension involvement to the pelvic sidewall than did patients in the nonextended surgical group.

Treatment details

Details of EBRT and of concomitant and adjuvant CT followed standards previously described (14). Perioperative EBRT (preoperative, n = 19; postoperative, n = 9) was delivered with megavoltage equipment (6-15 MV) and was begun within 24 hours of CT administration (n = 27, 96%). Conformal 3-dimensional radiation therapy was planned; fields were arranged taking into account doses delivered to normal tissues during radiation therapy for primary tumor. However, no specific dose−volume constraints were indicated by the treatment protocol. A total median dose of 45 Gy (range, 45-50.4 Gy), 1.8 Gy/5 days/week for patients not previously irradiated (n = 22) and 30.6 Gy (range, 21.6-30.6 Gy), 1.8 Gy/5 days/week for patients previously irradiated (n = 6) was prescribed to the isodose line, which covered the planning target volume (PTV) to obtain a homogeneity ranging between +5% and −5% of the prescribed dose. PTV was defined as LR (gross target volume, GTV) plus 2 cm of radial margin for preoperative EBRT and surgical tumor bed (clinical target volume, CTV) plus 2 cm of radial margin for postoperative EBRT patients. Chemotherapy concomitant schedule consisted of oral fluoropirimidine (Tegafur), 1.2 g/day. Patients had a 4-week rest after surgery and then could receive additional adjuvant CT (n = 30, 50%). Extended surgical (n = 38) procedures (4-6 weeks before or after perioperative treatment) consisted of lateral extended endopelvic resection (n = 6, 16%), posterior exenteration (n = 6, 16%), total pelvic exenteration (n = 9, 23%), sacrectomy (n = 6, 16%), or sacroexenteration (n = 11, 29% [posterior, n = 3; total, n = 8]). Nonextended surgical procedures were associated with low anterior resection (n = 8, 36%), ultralow anterior resection (n = 3, 14%), and abdominoperineal resection (n = 11, 50%) together with LR resection. The institutional IOERT program is performed in a nondedicated linear accelerator with outpatient radiation therapy activity. After surgery and before pelvic reconstruction, 10 to 15 Gy (median, 12.5 Gy) were delivered in a single fraction to a 1-field (n = 53, 88%) or 2-field (n = 7, 12%) PTV, using a median

Table 1 Patient, tumor, and treatment characteristics

Characteristics	All patients n=60 (%)	Extended surgery n=38 (%)	Nonextended surgery n=22 (%)	*P* value
Patient variables				
Median age, y (range)	55.7 (35-79)	57.9 (35-73)	54.2 (35-79)	.63
Sex				
M/F	33 (55)/27 (45)	21/17	12/10	.96
Karnofsky performance status				
≥90/<90	22 (37)/38 (63)	14/24	8/14	.97
Median interval from primary to LR, mo (range)	27.2 (3-158)	26.1 (3-98)	28.1 (5-158)	.89
Macroscopic tumor variables				
Extent of infiltration of recurrence on pelvic sidewall: F0/F1/F2/F3/F4	2 (3)/17 (28)/7 (12)/16 (27)/18 (30)	0/0/4/16/18	2/17/3/0/0	<.001
Pelvic relapse topography: posterior/posterolateral/ anterocentral	32 (53)/20 (33)/8 (14)	23/11/4	9/9/4	.33
Maximum recurrent tumor diameter, ≥5 cm vs <5 cm	23 (38)/37 (62)	17/21	6/16	.25
Median recurrent tumor size, cc (range)	4.5 (2-9)	4.8 (2-9)	4.1 (2-6)	.35
Tumor fragmentation: yes vs no	26 (43)/34 (57)	18/20	8/14	.41
Microscopic tumor variables				
Initial primary tumor histologic grade: I-II vs III	52 (87)/8 (13)	3/35	5/17	.10
Margin status: R0 vs R1	38 (63)/22 (37)	25/13	13/9	.61
Recurrent tumor lymph node status: metastatic vs nonmetastatic	8/(13)/52 (87)	4/34	4/18	.40
Surgical variables				
Multiorgan resection: yes vs no	26 (43)/34 (57)	26/12	0/22	<.001
Bone resection: yes vs no	17 (28)/43 (72)	17/21	0/22	.001
Soft tissue resection: yes vs no	23 (38)/37 (62)	23/15	0/22	<.001
Radiation therapy and chemotherapy variables				
Adjuvant chemotherapy initial primary tumor: yes vs no	36 (60)/24 (40)	25/13	11/11	.23
EBRT for initial primary tumor: yes vs no	30 (50)/30 (50)	20/18	10/12	.59
Adjuvant chemotherapy for recurrent tumor: yes vs no	30 (50)/30 (50)	21/17	9/13	.13
EBRT for recurrent tumor: yes vs no	28 (47)/32 (53)	15/23	13/9	.14
Acute toxicity ≥3				.44
Gastrointestinal fistula	4 (7)	2	2	
Soft tissue abscess	1 (2)	1	0	
Wound infection	5 (8)	3	2	
Peripheral neuropaathy	5 (8)	3	2	
Cardiac	5 (8)	2	3	
Pulmonary	5 (8)	3	2	
Chronic toxicity ≥3				.23
Gastrointestinal	6 (10)	6	4	
Peripheral neuropathy	6 (10)	6	4	
Perioperative mortality: yes vs no	3 (8)/0 (0)	3	0	.18

Abbreviation: EBRT = external beam radiation therapy.
Multiorgan resection (≥2 pelvic organs): posterior exenteration (n=6), total pelvic exenteration (n=9), sacroexenteration (n=11).
Bone resection: laterally extended endopelvic resection (LEER) (n=1), sacrectomy (n=6), sacroexenteration (n=11).
Soft tissue resection: LEER (n=6), sacrectomy (n=6), sacroexenteration (n=11).
* χ^2 or Mann-Whitney test.

energy of 12 MeV (range, 6-18 MeV). Intraoperative margin status was assessed using frozen pathologic sections; patients with R0 resections received an IOERT dose of 10 to 12.5 Gy, and patients with R1 resections received 15 Gy. Beveled (15° to 45°) Lucite circular applicators (size range, 5-15 cm) were adjusted to collimate the target surface air gap, allowing dosimetric adaptation and uniform dose distribution. CT-guided treatment has been available since 2008 (15). Table 2 shows macroscopic and microscopic histologic characteristics and their relationship with IOERT technical parameters.

Follow-up and toxicity evaluation

All patients were scheduled to be followed up according to the institutional protocol every 3 months after treatment completion

Table 2 Correlations between macroscopic/microscopic pathology characteristics and IOERT technical parameters

Pathology/IOERT	Surgical specimens	Applicator size Median (range)	IOERT dose (Gy) Median (range)	IOERT energy (MeV) Median (range)
Total number of fragments				
1	34	6 (5-10)	12.5 (10-15)	10 (6-15)
2	10	6 (5-12)	12.5 (10-15)	12 (6-18)
3	8	7 (5-12)	12.5 (10-15)	12 (6-18)
4	5	8 (6-12)	12.5 10-12.5)	12 (6-12)
5-6	3	7 (5-10)	12.5 (12.5-15)	15 (10-18)
Tmax size (cm)				
2.0-3.0	33	6 (5-9)	12.5 (10-15)	9 (6-15)
3.1-5.0	11	6 (5-12)	12.5 (10-15)	12 (6-15)
5.1-9.0	16	8 (7-12)	12.5 (10-15)	12 (6-18)

Abbreviation: IOERT = intraoperative electron beam radiation therapy.

for the initial 3 years and every 6 months for 3 additional years thereafter. Patients were restaged 4 weeks after RT (before surgery) and routinely every 6 months with CT scan of the abdomen and pelvis. Assessment of surgical complications was done according to the Clavien-Dindo classification (16). Acute and toxicities were evaluated according to Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer score (17).

Statistical analysis

The data collected were analyzed by SPSS (version 19.0) statistical software. The primary endpoint of the analysis was locoregional control (LRC). Secondary endpoints were OS, disease-free survival (DFS), and distant metastases-free survival (DMFS). The Kaplan-Meier method was used to estimate the probabilities of LRC, OS, DFS, and DMFS. Potential associations were assessed in univariate and multivariate analyses by the Cox proportional hazards model (2-sided P test $\leq .05$). Adjustment was performed for factors significant on univariate analysis (2-sided P test $<.10$).

Results

The median follow-up time for the entire cohort of patients was 36 months (range, 2-189 months). The median follow-up time for surviving patients was 77 months (range, 21-189 months). No patients were lost to follow-up. Twenty patients remained alive at the time of analysis. Of the 40 deceased patients, 33 (88%) died of proven cancer progression, 3 (5%) died of treatment toxicity, and 4 (7%) died of causes unrelated to their cancer or treatment. Twenty-eight patients had a second LRR (47%), 28 of the original 60 patients (47%) experienced distant metastases (sites of distant metastases including lung [n = 12], liver [n = 9], peritoneum [n = 5], bone [n = 1], and brain [n = 1]), and 15 (25%) patients had synchronous local and distant progression. Eight of the 28 (29%) patients who had a second LRR underwent rescue operation with a second surgical procedure, which achieved 3 long-term survivors (49, 90, and 170 months, respectively).

The OS survival for the study population at 1, 3, and 5 years was 78%, 53%, and 43%, respectively (Fig. 1). Univariate Cox proportional hazard analyses showed that R1 resection ($P = .004$) was associated with inferior OS. No tumor fragmentation was associated with a trend toward superior OS ($P = .07$) (Table 3). After adjustment for other covariates, R1 resection and no tumor fragmentation showed a significant association with OS (Table 4). The 1-year, 3-year, and 5-year rates of LRC were 86%, 52%, and 44%, respectively (Fig. 1). On univariate analysis, patients who did not receive EBRT (5-year LRC, 56.2% vs 32.0%, $P = .02$) and R1 resection (5-year LRC, 55.7% vs 19.0%, $P = .02$) were at a significantly higher risk of LRR (Table 3 and Fig. 2A, B). Patients without tumor fragmentation (Fig. 2C) and age older than 55 years had a lower risk of LR relapse (Table 3). We found on multivariate analysis that R1 resection, EBRT integrated at the time of LRR, nonmetastatic lymph nodes, and no tumor fragmentation retained significance (Table 4). We then evaluated patients with and without radical resection separately. For the subset with R0 resection (n = 38), patients who did not receive EBRT experienced a significantly higher risk of local relapse in univariate analysis (HR 3.23, CI 95% 1.0-9.96; $P = .05$) (Fig. 2D). Alternatively, for the subset with R1 resection (n = 22), univariate analysis did not showed that patients not receiving EBRT had an increased risk for a second local relapse (HR 2.28, CI 95% 0.74-7.02; $P = 0.15$). When tumor fragmentation was evaluated in patients with and without EBRT to the pelvic LRR, we found that only for the subset with tumor fragmentation (n = 26), those not receiving EBRT showed worse LRC (HR 2.84, CI 95% 1.08-8.04; $P = 0.04$) (Fig. 2E). For patients without tumor fragmentation (n = 34), this analysis did not reach statistical significance (HR 1.84, CI 95% 0.61-5.51; $P = .28$). In regard to patients with extended surgical resection (n = 38), not receiving EBRT increased the risk of LRR (HR 0.05, CI 95% 0.03-0.67; $P = .014$). Finally, we found no difference in the LRR rate among patients with extended surgical resection and nonextended surgery (HR 1.15, CI 95% 0.55-2.44; $P = .71$) (Fig. 2F). DMFS and DFS at 1, 3, and 5 years were 85%, 52%, and 43%; and 81%, 46%, and 37%, respectively (Fig. 1). Univariate analyses showed that no tumor fragmentation was associated with a lower risk of DMFS (Table 3). After adjustment for other covariates, no tumor fragmentation retained a favorable significance (Table 4). In regard to DFS, no tumor fragmentation was the only factor significantly associated with DFS on multivariate analysis.

Causes of acute and chronic toxicity were estimated as multifactorial (18). Overall, 25 patients (42%) had grade ≥ 3 acute toxicity: gastrointestinal fistula (n = 4, grade 3), soft tissue abscess (n = 1, grade 3), wound infection (n = 3, grade 3; n = 2; grade 5), peripheral

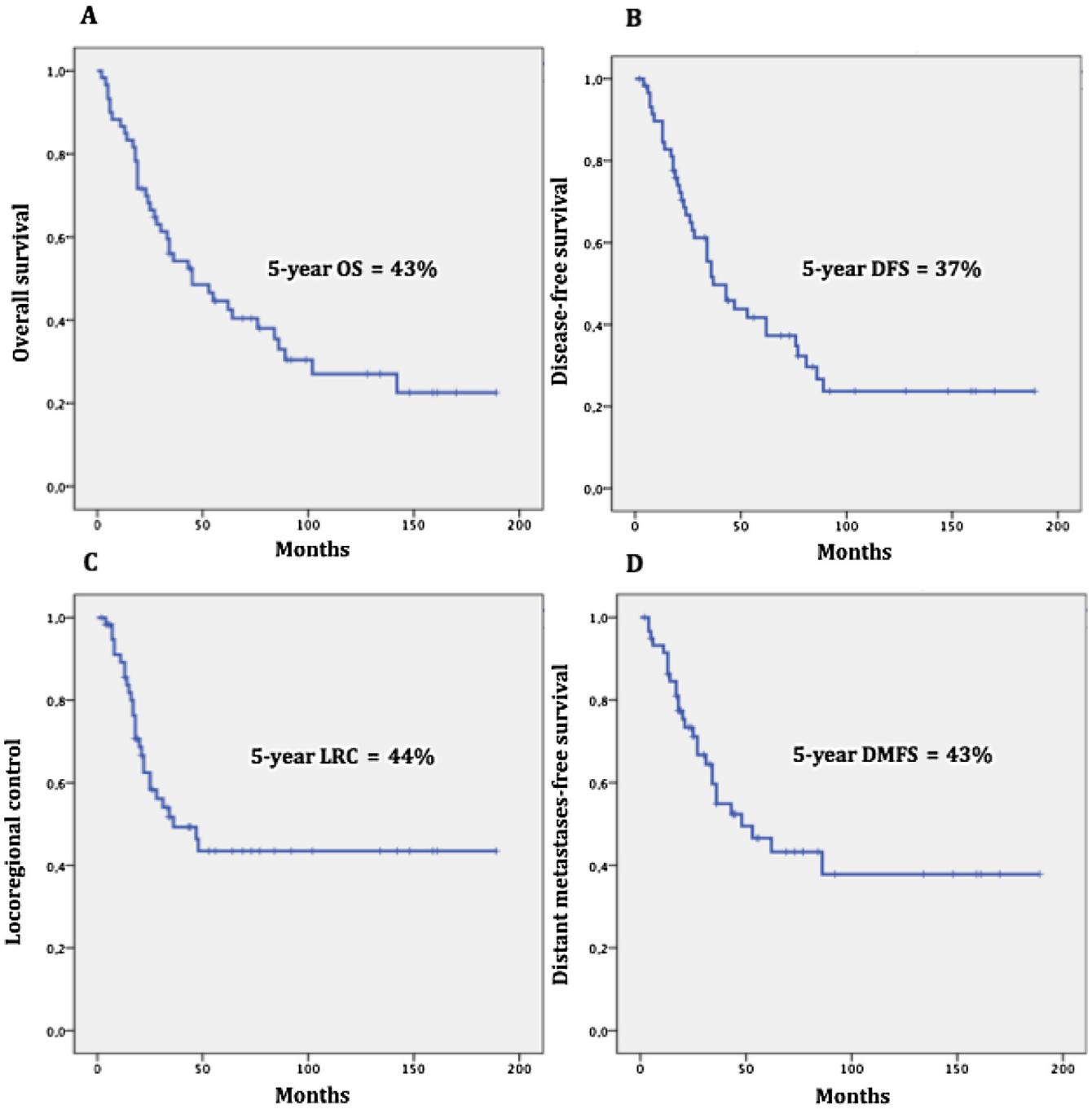


Fig. 1. Kaplan-Meier curves for all 60 patients for overall survival (OS) (A), disease-free survival (DFS) (B), local-regional control (LRC) (C), and distant metastasis-free survival (DMFS) (D).

neuropathy (n = 4, grade 3; n = 1, grade 4), cardiac (n = 4, grade 3; n = 1, grade 5), and pulmonary (n = 5, grade 3). Twelve patients (20%) experienced grade ≥3 chronic toxicity: gastrointestinal (n = 4, grade 3; n = 2, grade 4); neurologic (n = 3, grade 3; n = 3, grade 4). Overall treatment mortality was 5%: (n = 3 [wound infection-sepsis, n = 2; cardiac, n = 1]). No death resulting from treatment occurred. In regard to overall perioperative complications, we found that patients treated with extended surgery had higher rates of perioperative complications than did patients treated with nonextended surgery: 73.7% (n = 28) versus 45.5% (n = 10) ($P = .03$); longer median time of surgery: 365 minutes (range, 145-750 minutes) versus 260 minutes (range, 100 vs 465 minutes) ($P = .02$); longer median time in the intensive care unit: 2 days (range, 0-18 days) versus 0 days (range, 0-2 days) ($P = .004$); and longer median time of hospitalization: 17 days (range, 1-156 days) versus 10 days (range, 1-50 days) ($P = .005$). In relation to perioperative mortality, no difference was found: 7.8% (n = 3) versus 0% (n = 0) ($P = 0.18$) (Table 1).

Discussion

Our relevant findings can be summarized as follows. First, we found that extended surgical resection compensates for adverse LR features. Second, we found that not adding EBRT to surgery

Table 3 Univariate analyses of associations between patient, tumor, treatment, and pathologic characteristics and survival

		Locoregional control			Distant metastases-free survival			Disease-free survival			Overall survival		
Parameter	Variable	HR	CI 95%	*P* value	HR	CI 95%	*P* value	HR	CI 95%	*P* value	HR	CI 95%	*P* value
Patients													
Age, y	≤55	1.0	0.22-1.0	.05	1.0	0.35-1.60	.46	1.0	0.39-1.40	.74	1.0	0.47-1.64	.68
	>55	0.47			0.75			0.74			0.87		
Sex	M	1.0	0.43-1.92	.81	1.0	0.55-2.45	.71	1.0	0.67-2.41	.46	1.0	0.46-1.62	.65
	F	0.91			1.16			1.27			0.86		
Karnofsky performance status	>90	1.0	0.50-2.29	.85	1.0	0.61-2.39	.48	1.0	0.67-2.50	.44	1.0	0.75-2.86	.26
	≤90	1.08			1.22			1.29			1.47		
Macroscopic surgical specimen													
Extent of infiltration on pelvic sidewall	F0-F2	1.0	0.50-2.22	.88	1.0	0.53-2.37	.77	1.0	0.61-2.17	.87	1.0	0.60-2.11	.71
	F3-F4	1.06			1.12			1.15			1.13		
Pelvic relapse topography	Posterior	1.0	0.86-4.49	.10	1.0	0.86-4.83	.10	1.0	0.83-3.63	.10	1.0	0.77-2.96	.23
	Posterolateral	2.01	0.26-3.15	.88	2.16	0.22-2.67	.68	1.84	0.26-2.28	.62	1.51	0.21-1.85	.41
	Anterolateral	0.88			0.77			0.62			0.63		
Recurrent tumor size, cc	>5	1.0	0.32-1.42	.29	1.0	0.35-1.71	.53	1.0	0.33-1.26	.20	1.0	0.35-1.30	.24
	≤5	0.67			0.77			0.64			0.68		
Recurrent tumor Fragmentation	Yes	1.0	0.18-0.82	.01	1.0	0.14-0.66	.002	1.0	0.28-1.0	.05	1.0	0.3-1.05	.07
	No	0.38			0.31			0.52			0.56		
Microscopic surgical specimen													
Primary tumor histologic grade	I-II	1.0	0.65-4.52	.28	1.0	0.73-4.39	.24	1.0	0.82-4.25	.14	1.0	0.66-3.38	.34
	III	1.71			1.78			1.86			1.49		
Recurrent tumor Margin status	R0	1.0	1.08-4.82	.03	1.0	0.82-4.11	.14	1.0	0.95-3.53	.07	1.0	1.36-4.80	.004
	R1	2.28			1.83			1.83			2.55		
Recurrent tumor Lymph node	Metastatic	1.0	0.02-1.16	.07	1.0	0.16-1.76	.29	1.0	0.19-1.56	.27	1.0	0.22-1.72	.35
	Nonmetastatic	0.16			0.53			0.56			0.61		
Surgery													
Extended surgery	Yes	1.0	0.41-1.83	.71	1.0	0.44-2.02	.89	1.0	0.40-1.48	.44	1.0	0.43-1.54	.54
	No	0.87			0.95			0.78			0.82		
Multiorgan resection	Yes	1.0	0.40-1.97	.78	1.0	0.34-1.54	.41	1.0	0.01-5.21	.74	1.0	0.42-1.56	.53
	No	0.89			0.73			0.71			0.81		
Vascular resection	Yes	ND											
	No												
Bone resection	Yes	1.0	0.24-1.65	.34	1.0	0.13-1.09	.07	1.0	0.33-1.91	.94	1.0	0.41-1.72	.61
	No	0.63			0.38			0.92			0.83		
Soft tissue resection	Yes	1.0	0.31-1.61	.42	1.0	0.31-1.52	.36	1.0	0.21-1.11	.09	1.0	0.41-1.65	.58
	No	0.71			0.68			0.48			0.82		
EBRT and CT treatment													
Primary tumor EBRT treatment	Yes	1.0	0.38-1.68	.55	1.0	0.44-1.96	.85	1.0	0.48-1.69	.75	1.0	0.39-1.38	.33
	No	0.79			0.93			0.91			0.73		
Primary tumor adjuvant CT	Yes	1.0	0.49-2.21	.91	1.0	0.73-3.81	.22	1.0	0.53-2.1	.93	1.0	0.41-1.47	.45
	No	1.04			1.67			1.1			0.79		
Recurrent tumor EBRT treatment	Yes	1.0	1.10-5.21	.03	1.0	0.51-2.25	.86	1.0	0.69-2.44	.43	1.0	0.72-2.55	.35
	No	2.40			1.07			1.30			1.35		
Recurrent tumor adjuvant CT	Yes	1.0	0.85-4.05	.12	1.0	0.61-2.75	.51	1.0	0.61-2.17	.66	1.0	0.61-2.19	.66
	No	1.86			1.29			1.15			1.16		

Abbreviations: CI = confidence interval; CT = computed tomography; EBRT = external beam radiation therapy; HR = hazard ratio.

Table 4 Factors associated with locoregional control, distant metastases-free survival, disease-free survival, and overall survival in multivariate analyses

		Locoregional control			Distant metastases-free survival			Disease-free survival			Overall survival		
Parameter	Variable	HR	CI 95%	*P* value	HR	CI 95%	*P* value	HR	CI 95%	*P* value	HR	CI 95%	*P* value
Tumor fragmentation	Yes	1.0	0.23-0.95	.05	1.0	0.16-0.75	.007	1.0	0.29-1.0	.05	1.0	0.25-0.91	.02
	No	0.49			0.35			0.54			0.48		
Margin status	R0	1.0	1.04-4.53	.05	-	-	-	-	-	-	1.0	1.51-5.57	.001
	R1	2.09									2.90		
Lymph node	Metastatic	1.0	0.05-0.72	.03	-	-	-	-	-	-	-	-	-
	Nonmetastatic	0.18											
Recurrent tumor EBRT treatment	Yes	1.0	1.05-5.36	.04	-	-	-	-	-	-	-	-	-
	No	2.38											

Abbreviations: CI = confidence interval; HR = hazard ratio; RT = radiation therapy.
Multivariate analysis was redone and was carried out backwise with preassigned *P* values of >.05 controlling step removal.

and IOERT in patients with LRRC was significantly associated with a decreased risk of LRC. Interestingly, this maintained significance when patients with radical resection and tumor fragmentation were analyzed separately. Finally, we found that patients with no tumor fragmentation had a decreased probability of LR, DF, and overall mortality and that patients undergoing nonradical resection had lower rates of LRC and OS. Although the number of studies assessing patients with LRRC undergoing rescue operation with surgery, intraoperative radiotherapy (IORT), and EBRT is limited, the major results reported in the present article (5-year LRC 44% and OS 43%) are comparable with those reported in the literature (5-year LRC 30%-75% and OS 20%-50%) (6-11). Haddock et al (11) reported the largest institutional expert experience with IOERT for the rescue of recurrent colorectal cancer (n=607). Although detailed data on the site of recurrence and rescue are not provided, the outcome was more favorable for recurrence in the colon than in the rectum (5-year survival 34% vs 28%, $P=.07$). Kusters et al (10) analyzed 170 patients with LRRC who underwent multimodality treatment with preoperative CRT, elective radical surgery, and IOERT. The worst outcomes were seen in presacral recurrences: 28% complete resections and 19% 5-year survival ($P=.03$). The most favorable outcomes were observed for anastomotic LRRC, with 77% R0 resections and 60% 5-year survival ($P=.04$). Consistently, we also found that patients with nonradical resections had worse overall outcomes than did patients with radical resections. Moreover, patients with nonradical resections treated without EBRT had worse LRC than did those who received EBRT treatment. In a previous report (19), we evaluated the feasibility and long-term outcome of surgery combined with IOERT in patients with recurrent oligotopic extrapelvic cancer (n=28). With a median follow-up time of 39 months, we found that LR was significantly affected by microscopic cancer in more than 50% of specimen fragments (38% vs 9%, $P=.02$). In the current analysis, no tumor fragmentation was associated with an improved chance of LRC, DMFS, and OS. In a subset analysis, patients with tumor fragmentation not receiving EBRT had a decreased probability of LRC. To this end, several studies have shown that pelvic reirradiation with a low total dose of EBRT is acceptably tolerated, with moderate rates of late toxicity, and may help promote pelvic control (13). In our report, patients being reirradiated (n=7) did not have worse survival outcomes, probably because 5 of 7 patients had R0 resections, thus making it difficult to detect an advantage among patients without reirradiation (n=21). Valentini et al (13) reported in patients with LRRC who had previously received pelvic EBRT a 5-year overall survival of 39%, despite 87.4% of patients having sidewall involvement disease (35% R0 resections; 64% were alive at 5 years). Our finding that perioperative EBRT to LRRC patients was associated with improved outcomes is consistent with prior studies (13, 20). Pacelli et al (20) reported in a subset analysis of LRRC patients with potentially curative resection (R0 to R1) that preoperative chemoradiation therapy improved 5-year OS (44.6 vs 25.8%, $P=.012$).

However, data regarding the optimal treatment sequence and the contribution of an EBRT component to this clinical scenario remain to be elucidated.

In regard to treatment-related toxicity, the acceptable tolerance and rate of postsurgical complications suggest that a multimodality approach with an extended surgical component for LRRC is feasible with tolerable risks and without prohibitive long-term side effects.

We acknowledge several limitations of our study. First, the population was heterogeneous, having been treated over 16 years and receiving different treatment combinations. Although we did observe a significant association between EBRT treatment and LRC after adjustment for several potential confounding factors, we certainly acknowledge the presence of a selection bias for patients referred for radiation therapy to a higher dose. A systematic method of follow-up, including imaging, would be optimal to evaluate patterns of failure after radiation therapy, although, given the prospective nature of this analysis, consistent homogeneous imaging did not occur in a proportion of patients. Therefore, a significant number of patients with distant-only recurrence may not have undergone optimal imaging of the pelvis at the time of recurrence. Finally, it must be emphasized that systemic therapy plays an important role in the management of LRRC. Up-front chemotherapy followed by either switch/continuation maintenance or observation in different combinations with local therapy should be tested in the scenario of a clinical trial if possible.

In conclusion, we found that LRRC patients who received EBRT and IOERT could be treated safely and had improved rates of LRC on both univariate and multivariate analysis. We also found that patients with radical resections and no tumor fragmentation experienced the largest benefit with EBRT treatment,

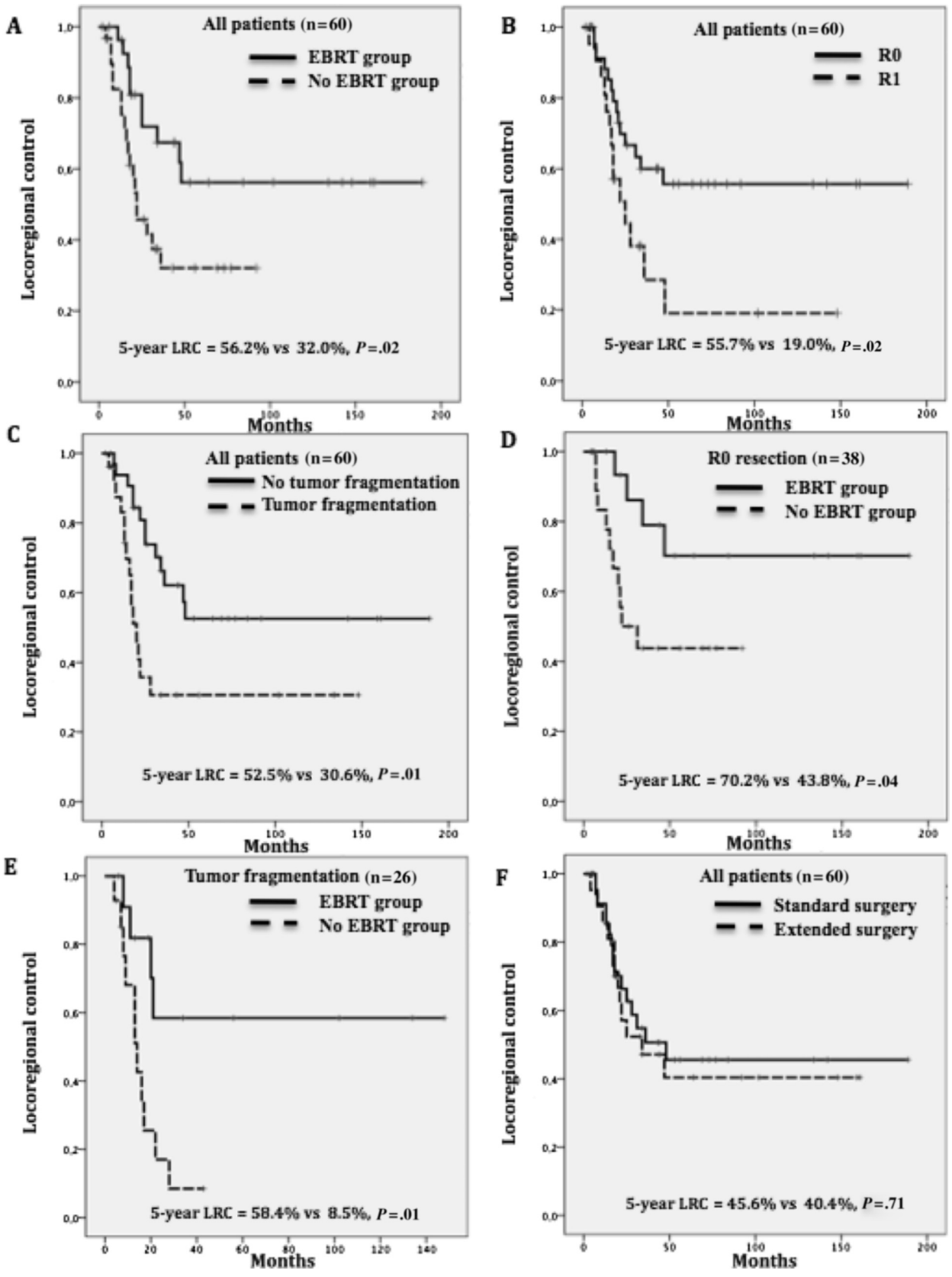


Fig. 2. Locoregional control according to external beam radiation therapy (EBRT) to the recurrent tumor (A), margin status (B), tumor fragmentation (C), EBRT to the recurrent tumor in R0 patients (n=38) (D), EBRT to the recurrent tumor in patients with tumor fragmentation (n=26) (E), and surgical (standard/extended) resection (F).

although a level of adverse prognostic features (nonradical resections) might be compensated by the addition of EBRT. Our results suggest that a subgroup of patients with LRRC could benefit from intensive local treatment to the LR.

References

1. Heald RJ, Moran BJ, Ryall RDH, et al. Rectal cancer: The Basingstoke experience of total mesorectal excision, 1978−1997. *Arch Surg* 1998;133:894-899.
2. Sauer R, Liersch T, Merkel S, et al. Preoperative versus postoperative chemoradiotherapy for locally advanced rectal cancer: Results of the German CAO/ARO/AIO-94 randomized phase III trial after a median follow-up of 11 years. *J Clin Oncol* 2012;30:1926-1933.
3. van Gijn W, Marijnen CA, Nagtegaal ID, et al. Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer: 12-year follow-up of the multicentre, randomised controlled TME trial. *Lancet Oncol* 2011;12:575-582.
4. Wanebo HJ, Antoniuk P, Koness RJ, et al. Pelvic resection of recurrent rectal cancer: Technical considerations and outcomes. *Dis Colon Rectum* 1999;42:1438-1448.
5. Hellman S, Weichselbaum RR. Oligometastases. *J Clin Oncol* 1995; 13:8-10.
6. Roeder F, Goetz JM, Habl G, et al. Intraoperative electron radiation therapy (IOERT) in the management of locally recurrent rectal cancer. *BMC Cancer* 2012;12:592.
7. Hahnloser D, Nelson H, Gunderson LL, et al. Curative potential of multimodality therapy for locally recurrent rectal cancer. *Ann Surg* 2003;237:502-508.
8. Dresen RC, Gosens MJ, Martijn H, et al. Radical resection after IORT-containing multimodality treatment is the most important determinant for outcome in patients treated for locally recurrent rectal cancer. *Ann Surg Oncol* 2008;15:1937-1947.
9. Wells BJ, Stotland P, Ko MA, et al. Results of an aggressive approach to resection of locally recurrent rectal cancer. *Ann Surg Oncol* 2007; 14:390-395.
10. Kusters M, Dresen RC, Martijn H, et al. Radicality of resection and survival after multimodality treatment is influenced by subsite of locally recurrent rectal cancer. *Int J Radiat Oncol Biol Phys* 2009;75: 1444-1449.
11. Haddock MG, Miller RC, Nelson H, et al. Combined modality therapy including intraoperative electron irradiation for locally recurrent colorectal cancer. *Int J Radiat Oncol Biol Phys* 2011;79: 143-150.
12. Braendengen M, Tveit KM, Berglund A, et al. Randomized phase III study comparing preoperative radiotherapy with chemoradiotherapy in nonresectable rectal cancer. *J Clin Oncol* 2008;26: 3687-3694.
13. Valentini V, Morganti A, Gambacorta MA, et al. Preoperative hyperfractionated chemoradiation for locally recurrent rectal cancer in patients previously irradiated to the pelvis: A multicentric phase II study. *Int J Radiat Oncol Biol Phys* 2006;64: 1129-1139.
14. Gunderson LL, Willett CG, Calvo FA, et al. editors. Intraoperative irradiation: Techniques and results. 2nd ed. Springer New York: Humana Press; 2011.
15. Pascau J, Santos Miranda JA, Calvo FA, et al. An innovative tool for intraoperative electron beam radiotherapy simulation and planning: Description and initial evaluation by radiation oncologists. *Int J Radiat Oncol Biol Phys* 2012;83:287-295.
16. Clavien PA, Barkun J, de Oliveira ML, et al. The Clavien-Dindo classification of surgical complications: Five-year experience. *Ann Surg* 2009;250:187-196.
17. Cox JD, Stetz J, Pajak TF. Toxicity criteria of the Radiation Oncology Group (RTOG) and the European Organization for Research and Treatment of Cancer (EORTC). *Int J Radiat Oncol Biol Phys* 1995;31: 1341-1346.
18. Azinovic I, Calvo FA, Puebla F, et al. Long-term normal tissue effects of intraoperative electron radiation therapy (IOERT): Late sequelae, tumor recurrence, and second malignancies. *Int J Radiat Oncol Biol Phys* 2001;49:597-604.
19. Calvo FA, González ME, González-San Segundo C, et al. Surgery and intraoperative electron radiotherapy in recurrent or metastatic oligotopic extrapelvic cancer: Long-term outcome. *Eur J Surg Oncol* 2012; 38:955-961.
20. Pacelli F, Tortorelli A, Rosa F, et al. Locally recurrent rectal cancer: Prognostic factors and long-term outcomes of multimodal therapy. *Ann Surg Oncol* 2010;17:152-162.

ELSEVIER LICENSE
TERMS AND CONDITIONS

Nov 14, 2013

This is a License Agreement between Claudio V Sole ("You") and Elsevier ("Elsevier") provided by Copyright Clearance Center ("CCC"). The license consists of your order details, the terms and conditions provided by Elsevier, and the payment terms and conditions.

All payments must be made in full to CCC. For payment instructions, please see information listed at the bottom of this form.

Supplier	Elsevier Limited The Boulevard,Langford Lane Kidlington,Oxford,OX5 1GB,UK
Registered Company Number	1982084
Customer name	Claudio V Sole
Customer address	Americo Vespucio norte 1314 Santiago, 7603360
License number	3266730918688
License date	Nov 12, 2013
Licensed content publisher	Elsevier
Licensed content publication	International Journal of Radiation Oncology*Biology*Physics
Licensed content title	Prognostic Impact of External Beam Radiation Therapy in Patients Treated With and Without Extended Surgery and Intraoperative Electrons for Locally Recurrent Rectal Cancer: 16-Year Experience in a Single Institution
Licensed content author	Felipe A. Calvo,Claudio V. Sole,Pedro Alvarez de Sierra,Marina Gómez-Espí,Jose Blanco,Miguel A. Lozano,Emilio del Valle,Marcos Rodriguez,Alberto Muñoz-Calero,Fernando Turégano,Rafael Herranz,Luis Gonzalez-Bayon,Jose Luis García-Sabrido
Licensed content date	1 August 2013
Licensed content volume number	86
Licensed content issue number	5
Number of pages	9
Start Page	892
End Page	900
Type of Use	reuse in a thesis/dissertation
Portion	full article
Format	both print and electronic
Are you the author of this Elsevier article?	Yes
Will you be translating?	No

Title of your thesis/dissertation	Valor Pronóstico de la Radioterapia Externa en el Tratamiento Multidisciplinario de Pacientes con Oligorecurrencia Locoregional
Expected completion date	Dec 2014
Estimated size (number of pages)	120
Elsevier VAT number	GB 494 6272 12
Permissions price	0.00 USD
VAT/Local Sales Tax	0.00 USD / 0.00 GBP
Total	0.00 USD
Terms and Conditions	

INTRODUCTION

1. The publisher for this copyrighted material is Elsevier. By clicking "accept" in connection with completing this licensing transaction, you agree that the following terms and conditions apply to this transaction (along with the Billing and Payment terms and conditions established by Copyright Clearance Center, Inc. ("CCC"), at the time that you opened your Rightslink account and that are available at any time at http://myaccount.copyright.com).

GENERAL TERMS

2. Elsevier hereby grants you permission to reproduce the aforementioned material subject to the terms and conditions indicated.

3. Acknowledgement: If any part of the material to be used (for example, figures) has appeared in our publication with credit or acknowledgement to another source, permission must also be sought from that source. If such permission is not obtained then that material may not be included in your publication/copies. Suitable acknowledgement to the source must be made, either as a footnote or in a reference list at the end of your publication, as follows:

"Reprinted from Publication title, Vol /edition number, Author(s), Title of article / title of chapter, Pages No., Copyright (Year), with permission from Elsevier [OR APPLICABLE SOCIETY COPYRIGHT OWNER]." Also Lancet special credit - "Reprinted from The Lancet, Vol. number, Author(s), Title of article, Pages No., Copyright (Year), with permission from Elsevier."

4. Reproduction of this material is confined to the purpose and/or media for which permission is hereby given.

5. Altering/Modifying Material: Not Permitted. However figures and illustrations may be altered/adapted minimally to serve your work. Any other abbreviations, additions, deletions and/or any other alterations shall be made only with prior written authorization of Elsevier Ltd. (Please contact Elsevier at permissions@elsevier.com)

6. If the permission fee for the requested use of our material is waived in this instance, please be advised that your future requests for Elsevier materials may attract a fee.

7. Reservation of Rights: Publisher reserves all rights not specifically granted in the combination of (i) the license details provided by you and accepted in the course of this licensing transaction, (ii) these terms and conditions and (iii) CCC's Billing and Payment terms and conditions.

8. License Contingent Upon Payment: While you may exercise the rights licensed immediately upon issuance of the license at the end of the licensing process for the transaction, provided that you have disclosed complete and accurate details of your proposed use, no license is finally effective unless and until full payment is received from you (either by publisher or by CCC) as provided in CCC's Billing and Payment terms and conditions. If full payment is not received on a timely basis, then any license preliminarily granted shall be deemed automatically revoked and shall be void as if never granted. Further, in the event that you breach any of these terms and conditions or any of CCC's Billing and Payment terms and conditions, the license is automatically revoked and shall be void as if never granted. Use of materials as described in a revoked license, as well as any use of the materials beyond the scope of an unrevoked license, may constitute copyright infringement and publisher reserves the right to take any and all action to protect its copyright in the materials.

9. Warranties: Publisher makes no representations or warranties with respect to the licensed material.

10. Indemnity: You hereby indemnify and agree to hold harmless publisher and CCC, and their respective officers, directors, employees and agents, from and against any and all claims arising out of your use of the licensed material other than as specifically authorized pursuant to this license.

11. No Transfer of License: This license is personal to you and may not be sublicensed, assigned, or transferred by you to any other person without publisher's written permission.

12. No Amendment Except in Writing: This license may not be amended except in a writing signed by both parties (or, in the case of publisher, by CCC on publisher's behalf).

13. Objection to Contrary Terms: Publisher hereby objects to any terms contained in any purchase order, acknowledgment, check endorsement or other writing prepared by you, which terms are inconsistent with these terms and conditions or CCC's Billing and Payment terms and conditions. These terms and conditions, together with CCC's Billing and Payment terms and conditions (which are incorporated herein), comprise the entire agreement between you and publisher (and CCC) concerning this licensing transaction. In the event of any conflict between your obligations established by these terms and conditions and those established by CCC's Billing and Payment terms and conditions, these terms and conditions shall control.

14. Revocation: Elsevier or Copyright Clearance Center may deny the permissions described in this License at their sole discretion, for any reason or no reason, with a full refund payable to you. Notice of such denial will be made using the contact information provided by you. Failure to receive such notice will not alter or invalidate the denial. In no event will Elsevier or Copyright Clearance Center be responsible or liable for any costs, expenses or damage incurred by you as a result of a denial of your permission request, other than a refund of the amount(s) paid by you to Elsevier and/or Copyright Clearance Center for denied permissions.

LIMITED LICENSE

The following terms and conditions apply only to specific license types:

15. **Translation**: This permission is granted for non-exclusive world **English** rights only unless your license was granted for translation rights. If you licensed translation rights you may only translate this content into the languages you requested. A professional translator must perform all translations and reproduce the content word for word preserving the

integrity of the article. If this license is to re-use 1 or 2 figures then permission is granted for non-exclusive world rights in all languages.

16. **Website**: The following terms and conditions apply to electronic reserve and author websites:
Electronic reserve: If licensed material is to be posted to website, the web site is to be password-protected and made available only to bona fide students registered on a relevant course if:
This license was made in connection with a course,
This permission is granted for 1 year only. You may obtain a license for future website posting,
All content posted to the web site must maintain the copyright information line on the bottom of each image,
A hyper-text must be included to the Homepage of the journal from which you are licensing at http://www.sciencedirect.com/science/journal/xxxxx or the Elsevier homepage for books at http://www.elsevier.com , and
Central Storage: This license does not include permission for a scanned version of the material to be stored in a central repository such as that provided by Heron/XanEdu.

17. **Author website** for journals with the following additional clauses:

All content posted to the web site must maintain the copyright information line on the bottom of each image, and the permission granted is limited to the personal version of your paper. You are not allowed to download and post the published electronic version of your article (whether PDF or HTML, proof or final version), nor may you scan the printed edition to create an electronic version. A hyper-text must be included to the Homepage of the journal from which you are licensing at http://www.sciencedirect.com/science/journal/xxxxx . As part of our normal production process, you will receive an e-mail notice when your article appears on Elsevier's online service ScienceDirect (www.sciencedirect.com). That e-mail will include the article's Digital Object Identifier (DOI). This number provides the electronic link to the published article and should be included in the posting of your personal version. We ask that you wait until you receive this e-mail and have the DOI to do any posting.

Central Storage: This license does not include permission for a scanned version of the material to be stored in a central repository such as that provided by Heron/XanEdu.

18. **Author website** for books with the following additional clauses:
Authors are permitted to place a brief summary of their work online only.
A hyper-text must be included to the Elsevier homepage at http://www.elsevier.com . All content posted to the web site must maintain the copyright information line on the bottom of each image. You are not allowed to download and post the published electronic version of your chapter, nor may you scan the printed edition to create an electronic version.

Central Storage: This license does not include permission for a scanned version of the material to be stored in a central repository such as that provided by Heron/XanEdu.

19. **Website** (regular and for author): A hyper-text must be included to the Homepage of the journal from which you are licensing at http://www.sciencedirect.com/science/journal/xxxxx. or for books to the Elsevier homepage at http://www.elsevier.com

20. **Thesis/Dissertation**: If your license is for use in a thesis/dissertation your thesis may be submitted to your institution in either print or electronic form. Should your thesis be published commercially, please reapply for permission. These requirements include

permission for the Library and Archives of Canada to supply single copies, on demand, of the complete thesis and include permission for UMI to supply single copies, on demand, of the complete thesis. Should your thesis be published commercially, please reapply for permission.

21. **Other Conditions**:

v1.6

If you would like to pay for this license now, please remit this license along with your payment made payable to "COPYRIGHT CLEARANCE CENTER" otherwise you will be invoiced within 48 hours of the license date. Payment should be in the form of a check or money order referencing your account number and this invoice number RLNK501157800.
Once you receive your invoice for this order, you may pay your invoice by credit card. Please follow instructions provided at that time.

Make Payment To:
Copyright Clearance Center
Dept 001
P.O. Box 843006
Boston, MA 02284-3006

For suggestions or comments regarding this order, contact RightsLink Customer Support: customercare@copyright.com or +1-877-622-5543 (toll free in the US) or +1-978-646-2777.

Gratis licenses (referencing $0 in the Total field) are free. Please retain this printable license for your reference. No payment is required.

Strahlenther Onkol 2014 · 190:171–180
DOI 10.1007/s00066-013-0472-5
Received: 3 June 2013
Accepted: 16 September 2013
Published online: 6 December 2013

C.V. Sole[1, 2, 3, 7] · F.A. Calvo[1, 2, 7] · M.A. Lozano[1, 4, 7] · L. Gonzalez-Bayon[5, 7] · C. Gonzalez-Sansegundo[1, 4, 7] · A. Alvarez[4, 7] · S. Lizarraga[6, 7] · J.L. García-Sabrido[2, 5, 6]

[1] Department of Oncology, Hospital General Universitario Gregorio Marañón, Madrid
[2] School of Medicine, Complutense University, Madrid
[3] Service of Radiation Oncology, Instituto de Radiomedicina, Santiago
[4] Service of Radiation Oncology, Hospital General Universitario Gregorio Marañón, Madrid
[5] Service of General Surgery, Hospital General Universitario Gregorio Marañón, Madrid
[6] Department of Gynecology, Hospital General Universitario Gregorio Marañón, Madrid
[7] Institute of Research Investigation, Hospital General Universitario Gregorio Marañón, Madrid

External-beam radiation therapy after surgical resection and intraoperative electron-beam radiation therapy for oligorecurrent gynecological cancer

Long-term outcome

Historically a clinical state of metastasis termed 'oligometastases' has refered to restricted tumor metastatic capacity [1]. The implication of this concept is that local cancer treatments have a curative potential in a proportion of patients with metastases [1]. Conversely, up to one third of patients with gynecologic oligorecurrence have a rescue opportunity [2]. Long-term survival is rare (5-year overall survival 5%) for patients with pelvic sidewall involvement, pelvic or paraaortic lymph node recurrence treated with standard salvage therapy [3]. Oligorecurrent gynecological cancer (ORGC) encompasses a broad disease category, consistently it has been reported that some patients may benefit from intensive local therapy [4, 5, 6]. Clinical practice of expert institutions has shifted from nonintervention or palliative treatment to more intensive multimodal approaches [7, 8, 9, 10, 11, 12, 13]. Successful salvage treatment is highly dependent on the extent of radicality of the resection [13]. Due to close proximity or proven tumor invasion into adjacent unresectable structures, it is often questionable whether a complete negative resection margin is achieved. Therefore, a combined approach including additional local therapies could improve local control and survival [4, 5, 6, 7, 8, 9, 10, 11, 12, 13]. To the best of our knowledge, no randomized trials evaluating different treatment regimens have been published to date. In this context, we investigated outcomes and novel risk factors for a group of patients with ORGC with pelvic sidewall or paraaortic isolated lymph node recurrence treated with surgical resection and intraoperative electron-beam radiation therapy (IOERT) in high-risk areas (post-resection and pre-reconstruction) with or without external-beam radiation therapy (EBRT).

Materials and methods

Patient selection criteria

Treatment protocols were in compliance with hospital ethics and clinical practice guidelines. Subjects with pathologically confirmed ORGC with pelvic sidewall or paraaortic isolated lymph node recurrence (no other extra-pelvic disease) and Karnofsky score ≥70 were offered to participate in a developmental institutional treatment program that consisted of extended surgery, EBRT and IOERT to the tumor bed area at risk for residual disease. Tumor board considered for surgical approach and adjuvant chemotherapy (CT) recommendation: initial treatment characteristics, location, tumor resectability and clinical status of patients. All patients (n=61) were offered to participate in the institutional EBRT plus IOERT program, but 32 (52%) declined (patients who did not consent EBRT had greater concerns related to re-treatment toxicity or issues related to treatment efficacy). Two treatment strategies were operational along the period: 29 patients (48%) were treated according to a research protocol that consisted of EBRT, surgery and IOERT with or without adjuvant chemotherapy (EBRT group). The remaining 32 patients were treated with surgery plus IOERT, but without EBRT (non-EBRT group) and served as the control cohort. Prospective-

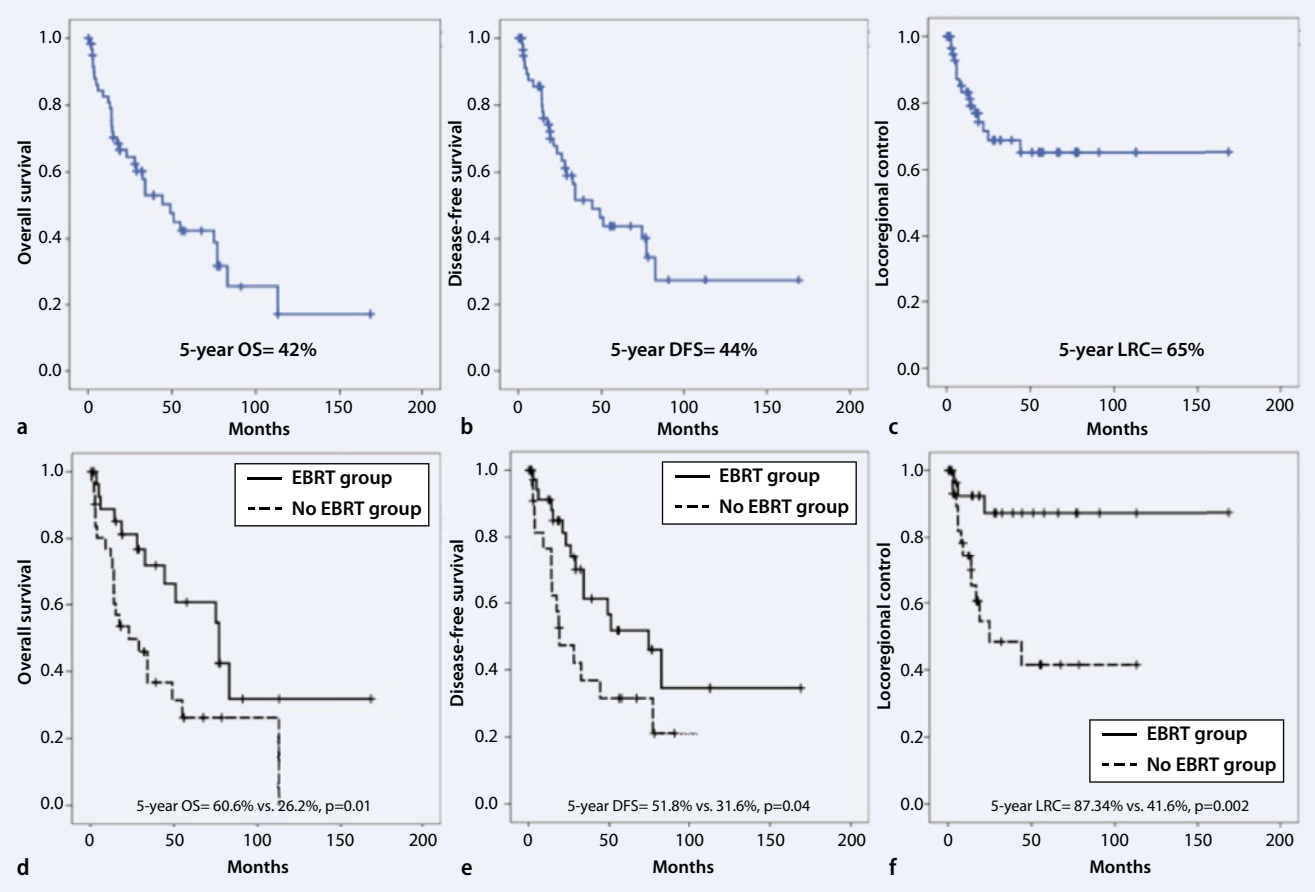


Fig. 1 ▲ Kaplan–Meier curves of all patients (n=61) for overall survival (**a**), disease-free survival (**b**) and local-regional control (**c**). Overall survival (**d**), disease-free survival (**e**) and local-regional control (**f**) according to EBRT treatment to the local relapse or not

ly collected hospital records of patients treated for ORGC between January 1995 and December 2012 were retrospectively reviewed. Patients were assessed at baseline by physical and gynecological examination, abdomen and pelvic computed tomography (CT) scan, pelvic magnetic resonance imaging (MRI) and chest X-ray. Patient and treatment characteristics are listed in **Tab. 1**. Compared treatment-based cohorts of patients were balanced between patients with pelvic (n=35, 57%) and paraaortic LR (n=26, 43%).

Treatment details

Details of EBRT, concomitant and adjuvant CT followed standards previously described [13]. Perioperative EBRT (preoperative [n=14]; postoperative [n=15]) was delivered with megavoltage equipment (6–15 MV) and was begun within 24 h of CT administration (n=25, 85%). Conformal three-dimensional radiotherapy for EBRT was planned; fields were arranged taking into account doses delivered to normal tissues during radiotherapy for primary tumor. However, no specific dose–volume constraints were indicated by the treatment protocol. A total median dose of 45 Gy (range 45–50.4 Gy, 1.8 Gy/5 days/week) for non-previously irradiated (n=16) patients and 30.6 Gy (range 21.6–30.6 Gy, 1.8 Gy/5 days/week] for previously irradiated patients (n=13), was prescribed to the isodose line which covered the planning target volume (PTV) to obtain a homogeneity ranging between ±5% of the prescribed dose. PTV was defined as LR (gross target volume, GTV) plus 2 cm of radial margin for preoperative EBRT and surgical tumor bed (clinical target volume, CTV) plus 2 cm of radial margin for postoperative EBRT patients. Chemotherapy concomitant schedule consisted of bolus intravenous cisplatin (75 mg/m^2/day 1 and d5, 2 cycles every 4 weeks) or none (ovarian recurrence).

Patients had a 4-week rest after surgery and then could receive additionally adjuvant CT (n=24, 39%). Surgical procedures (4–6 weeks before or after perioperative treatment) consisted for pelvic recurrence of anterior exenteration with lateral extended endopelvic resection (LEER) (n=1, 3%), LEER with vascular en bloc resection of the local recurrence (n=5, 14%), LEER alone (n=11, 31%), anterior exenteration (n=5, 14%), posterior exenteration (n=3, 9%), total pelvic exenteration (n=7, 20%) and posterior sacroexenteration, (n=3, 9%). For paraaortic LR surgical resection consisted of transperitoneal regional lymphadenectomy only (n=9, 26%) or associated with vascular (n=2, 8%) or soft tissue resection (n=15, 58%). The institutional IOERT program is performed in a non-dedicated linear accelerator with outpatient radiotherapy ac-

Abstract · Zusammenfassung

Strahlenther Onkol 2014 · 190:171–180 DOI 10.1007/s00066-013-0472-5

C.V. Sole · F.A. Calvo · M.A. Lozano · L. Gonzalez-Bayon · C. Gonzalez-Sansegundo · A. Alvarez · S. Lizarraga · J.L. García-Sabrido

External-beam radiation therapy after surgical resection and intraoperative electron-beam radiation therapy for oligorecurrent gynecological cancer. Long-term outcome

Abstract

Purpose. The goal of the present study was to analyze prognostic factors in patients treated with external-beam radiation therapy (EBRT), surgical resection and intraoperative electron-beam radiotherapy (IOERT) for oligorecurrent gynecological cancer (ORGC).
Patients and methods. From January 1995 to December 2012, 61 patients with ORGC [uterine cervix (52%), endometrial (30%), ovarian (15%), vagina (3%)] underwent IOERT (12.5 Gy, range 10–15 Gy), and surgical resection to the pelvic (57%) and paraaortic (43%) recurrence tumor bed. In addition, 29 patients (48%) also received EBRT (range 30.6–50.4 Gy). Survival outcomes were estimated using the Kaplan–Meier method, and risk factors were identified by univariate and multivariate analyses.
Results. Median follow-up time for the entire cohort of patients was 42 months (range 2–169 months). The 10-year rates for overall survival (OS) and locoregional control (LRC) were 17 and 65%, respectively. On multivariate analysis, no tumor fragmentation (HR 0.22; p=0.03), time interval from primary tumor diagnosis to locoregional recurrence (LRR) <24 months (HR 4.02; p=0.02) and no EBRT at the time of pelvic recurrence (HR 3.95; p=0.02) retained significance with regard to LRR. Time interval from primary tumor to LRR <24 months (HR 2.32; p=0.02) and no EBRT at the time of pelvic recurrence (HR 3.77; p=0.04) showed a significant association with OS after adjustment for other covariates.
Conclusion. External-beam radiation therapy at the time of pelvic recurrence, time interval for relapse ≥24 months and not multi-involved fragmented resection specimens are associated with improved LRC in patients with ORGC. As suggested from the present analysis a significant group of ORGC patients could potentially benefit from multimodality rescue treatment.

Keywords

Surgery · Intraoperative radiotherapy · Oligorecurrent gynecological cancer · External-beam radiation therapy · Survival

Externe Strahlentherapie nach Resektion und intraoperative Strahlentherapie mit Elektronen bei gynäkologischen Oligorezidiven. Langzeitergebnisse

Zusammenfassung

Hintergrund und Ziel. Ziel der vorliegenden Studie war die Analyse prognostischer Faktoren bei gynäkologischen Krebspatientinnen mit einem Oligorezidiv („oligorecurrent gynecological cancer", ORGC), welche mittels externer Radiotherapie („external-beam radiation therapy", EBRT), Chirurgie und intraoperativer Radiotherapie („intraoperative electron-beam radiotherapy", IOERT) behandelt wurden.
Patientinnen und Metoden. Zwischen Januar 1995 und Dezember 2012 wurden 61 gynäkologische Krebspatientinnen (52% Zervix, 30% Endometrium, 15% Ovar, 3% Vagina) an einem Oligorezidiv mittels IOERT (12,5 Gy; Spanne 10–15 Gy) und chirurgischer Resektion des pelvinen (57%) oder paraaortischen (43%) Tumorherds behandelt. Außerdem erhielten 29 Patientinnen eine EBRT (30,6–50,4 Gy). Die Überlebensrate wurde mit Hilfe der Kaplan-Meier-Methode ermittelt und Risikofaktoren wurden mittels univarianter und multivarianter Analyse identifiziert.
Ergebnisse. Die mediane Verlaufskontrollperiode für die Gesamtgruppe betrug 42 Monate (Spanne 2–169 Monate). Die 10-Jahres-Gesamtüberlebensrate und lokoregionale Kontrollrate betrugen jeweils 17 und 65%. In der multivarianten Analyse behielten die Abwesenheit von Tumorfragmentation (HR 0,22; p=0,03), eine Zeitspanne zwischen der primären Tumordiagnose und dem Lokalrezidiv <24 Monate (HR 4,02; p=0,02) und die Nichtverabreichung von EBRT im Falle eines pelvinen Lokalrezidivs (HR 3,95; p=0,02) ihre Signifikanz in Bezug auf das rezidivfreie Intervall. Eine Zeitspanne zwischen der primären Tumordiagnose und dem Lokalrezidiv <24 Monate (HR 2,32; p=0,02) und die Nichtverabreichung von EBRT im Falle eines pelvinen Lokalrezidivs (HR 3,77; p=0,04) behielten ihrerseits ihre Signifikanz in Bezug auf die Gesamtüberlebenszeit nach Justierung für andere Kovariablen.
Schlussfolgerungen. Die Verabreichung von EBRT im Falle eines pelvinen Lokalrezidivs, eine Zeitspanne ≥24 Monate bis zum Lokalrezidiv und eine einteilige, nichtfragmentierte Tumorresektion sagen eine signifikant bessere lokale Kontrolle bei ORCG-Patientinnen voraus. Hieraus lässt sich schließen, dass eine signifikante Untergruppe von ORGC-Patientinnen vorteilhaft mittels multimodaler Therapie behandelt werden könnte.

Schlüsselwörter

Chirurgie · Intraoperative Strahlentherapie · Oligorezidiv gynäkologischer Krebs · Externe Radiotherapie · Überleben

tivity. After surgery and before pelvic reconstruction, 10–15 Gy (median 12.5 Gy) were delivered in a single fraction to a one (n=42, 69%) or two-field (n=19, 31%) PTVs, using a median energy of 12 MeV (range 6–18 MeV). Intraoperative margin status was assessed using frozen pathologic sections, patients with R0 resections received an IOERT dose of 10–12.5 Gy and patients with R1 resections received 15 Gy. Beveled (15–45°) Lucite circular applicators (size range, 5–12 cm) were adjusted to collimate the target surface air gap, allowing dosimetric adaptation and uniform dose distribution. CT-guided IOERT treatment has been available since 2008 [14]. Macroscopic and microscopic histologic characteristics and their relationship with IOERT technical parameters are shown in **Tab. 2**.

Follow-up and toxicity evaluation

All patients were scheduled to be followed according to the institutional protocol every 3 months after treatment completion for the initial 3 years and every 6 months

Tab. 1 Patient, tumor and treatment characteristics

Characteristics	All patients n=61 (%)	Pelvic n=35 (%)	Paraaortic n=26 (%)	p value
Patient variables				
Median age (range)	55 (38–67)	53 (38–67)	57 (40–65)	0.18
Karnofsky performance status ≥90/<90	34 (56)/27 (44)	24 (69)/11 (31)	10 (38)/16 (62)	0.15
Time interval (months) from primary to LR (range) ≥24/<24	35 (57)/26 (43)	19 (54)/16 (46)	16 (62)/10 (38)	0.28
Macroscopic tumor variables				
Primary site Endometrial/uterine cervix/ovarian/vagina	18 (30)/32 (52)/9 (15)/2 (3)	7 (20)/20 (57)/6 (17)/2 (6)	11 (42)/12 (46)/3 (12)/0	0.14
Maximum recurrent tumor diameter ≥5 cm vs<5 cm	34 (56)/27 (44)	17 (45)/18 (55)	17 (65)/9 (35)	0.14
Tumor multifragmentation involvement Yes vs no	38 (62)/23 (38)	21 (60)/14 (40)	17 (65)/9 (35)	0.78
Microscopic tumor variables				
Initial primary tumor histologic grade I–II vs III	43 (70)/18 (30)	26 (74)/9 (26)	17 (65)/9 (35)	0.41
Histologic subtype Adenocarcinoma/squamous carcinoma	35 (57)/26 (43)	20 (57)/15 (43)	15 (58)/11 (42)	0.95
Margin status R0 vs R1	32 (52)/29 (48)	19 (54)/16 (46)	13 (50)/13 (50)	0.74
Surgical variables				
Bone resection Yes vs no	11 (18)/50 (82)	6 (17)/29 (83)	5 (19)/21 (81)	0.86
Vascular resection Yes vs no	7 (11)/54 (89)	5 (14)/30 (86)	2 (8)/24 (91)	0.56
Soft tisue resection Yes vs no	35 (57)/26 (43)	20 (57)/15 (43)	15 (58)/11 (42)	0.95
Radiation therapy and chemotherapy variables				
Surgical resection treatment for initial primary tumor Yes vs no	44 (72)/17 (28)	26 (74)/9 (26)	18 (69)/8 (31)	0.63
Adjuvant chemotherapy initial primary tumor Yes vs no	33 (54)/28 (46)	21 (60)/14 (40)	12 (46)/14 (54)	0.28
EBRT for initial primary tumor Yes vs no	40 (66)/21 (34)	25 (71)/10 (29)	16 (62)/10 (38)	0.25
Adjuvant chemotherapy for recurrent tumor Yes vs no	24 (39)/37 (61)	13 (37)/22 (63)	11 (42)/15 (58)	0.57
EBRT for recurrent tumor Yes vs no	29 (48)/32 (52)	16 (46)/19 (54)	13 (50)/13 (50)	0.74
IOERT dose ≥12.5 Gy vs<12.5 Gy	41 (67)/20 (33)	22 (63)/13 (37)	19 (73)/7 (23)	0.38
Hospitalization				
Median time (minutes) of surgery	428 (188–950)	452 (205–950)	409 (188–625)	0.31
Median time (days) admitted to the intensive care unit	2.5 (0–9)	2.5 (0–9)	2.3 (0–7)	0.41
Median time (days) of overall hospitalization	20 (4–138)	20 (4–138)	18 (4–56)	0.31
Toxicity				
RTOG Chronic toxicity ≥3 *Gastroinstestinal (fistula n=5; abscess n=3)* *Genitourinary (ureteral stenosis n=3)* *Nervous (peripheral neurophaty n=1)*	12 (20)	8 (23)	4 (15)	0.22

Tab. 1 Patient, tumor and treatment characteristics (Continued)

Characteristics	All patients n=61 (%)	Pelvic n=35 (%)	Paraaortic n=26 (%)	p value
Clavien–Dindo perioperative complications	34 (56)	20 (57)	14 (54)	0.62
RTOG Acute toxicity ≥3 *Gastroinstestinal (n=3)* *Genitourinary (n=5)* *Soft tissue (n=1)* *Wound infection (n=3)* *Cardiac (n=1)* *Pulmonary (n=1)*	23 (38)	14 (40)	9 (35)	0.79

EBRT external beam radiation therapy, *RTOG* Radiation Therapy Oncology Group.

Tab. 2 Correlations between macroscopic/microscopic pathology characteristics and IOERT technical parameters

Pathology/IOERT treatment	Surgical specimens	Applicator size	IOERT dose (Gy)	IORT energy (MeV)
		Median/range	Median/range	Median/range
Total number of involved fragments				
1	28	8/5–12	12.5/10–15	10/6–15
2	10	9/5–12	12.5/10–15	9/6–18
3	13	8/5–12	12.5/10–15	12/9–18
4–6	10	8/5–10	12.5/10–15	12/6–18
Tmax size (cm)				
1.0–2.0	8	5/5–12	12.5/12.5–15	12/6–18
2.1–4.0	19	8/5–10	12.5/10–15	12/6–18
4.1–7.0	19	8/5–10	12.5/10–15	12/6–15
7.1–11.0	15	10/7–12	12.5/10–12.5	10/6–15

Tmax tumoral maximal dimension.

for 3 additional years thereafter. Patients were restaged 4 weeks after RT (before surgery) and routinely every 6 months with CT scan of the abdomen and pelvis. Assessment of surgical complications was done according Clavien–Dindo classification [15]. Acute and late toxicities were evaluated according to Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer score [16].

Statistical analysis

Data collected was analyzed by using SPSS (version 19.0) statistical software. The primary endpoint of the analysis was locoregional control (LRC). Secondary endpoints were OS and disease-free survival (DFS). The Kaplan–Meier method was used to estimate the probabilities LRC, OS, DFS, and DMFS. Potential associations were assessed in univariate and multivariate analyses by using the Cox proportional hazards model (two-sided p test ≤0.05). Adjustment was performed for factors significant on univariate analysis (two-sided p test ≤0.05).

Results

Median follow-up time for the entire cohort of patients was 42 months (range 2–169). Median follow-up time for surviving patients was 56 months (range 3–169). No patients were lost of follow-up. In all, 27 patients were alive at the time of analysis. Of the 34 deceased patients, 27 (79%) died from proven cancer progression, 1 (3%) died from treatment toxicity, and 6 (18%) died from causes unrelated to their cancer or treatment. Sixteen patients had a second LRR (26%), 21 out of the original 61 patients (34%) developed distant metastases [sites of distant metastases including: lung (n=10), liver (n=6) and peritoneum (n=5); 7 (11%) patients had a synchronous local and distant progression] and the total recurrence rate was 49% [30 out of 61 patients, median time to any recurrence was 19 months (range 2–78)]. Six out of the 16 (38%) patients who had a second LRR were re-rescued with a second surgical procedure, achieving 3 long-term survivors (39, 45, and 56 months).

Overall survival for the study population at 5 and 10 years was 42 and 17%, respectively (**Fig. 1a**). On univariate analysis, time interval from primary tumor diagnosis to LR <24 months (p=0.01) and not receiving EBRT to the LR (p=0.02) were associated with inferior OS (**Tab. 3**). We found on multivariate analysis a time interval from primary tumor diagnosis to LR <24 months and not receiving EBRT at the time of LRR retained significance (**Tab. 4**).

Disease-free survival at 5 and 10 years was 44 and 28%, respectively (**Fig. 1b**). Univariate analyses showed that a time interval from primary tumor diagnosis to LR <24 months (p=0.007), paraaortic recurrence site (p=0.05), primary tumor grade 3 (p=0.02), and not receiving EBRT to the LR (p=0.05) were associated with a higher risk of overall metastases (**Tab. 3**). After adjustment for other covariates, primary tumor diagnosis to LR <24 months and not receiving EBRT to the LR, retained significance in regard to DFS (**Tab. 4**).

The 5- and 10-year rates of LRC were 65 and 65%, respectively (**Fig. 1c**). Univariate Cox proportional hazard analyses showed that time interval from primary tumor diagnosis to LR <24 months (p=0.03), squamous carcinoma histology (p=0.03) and not receiving EBRT to the LR (p=0.007) were associated with inferior LRC. No tumor multifragment involvement (fragments involved by tumor on pathology report) was associated with a superior likelihood of LRC

Tab. 3 Univariate analyses of associations between the patient, tumor, treatment, and pathologic characteristics and survival

Parameter	Variable	Locoregional control			Disease-free survival			Overall survival		
		HR	CI 95%	p value	HR	CI 95%	p value	HR	CI 95%	p value
Patients										
Age (years)	*≤55*	1.0	0.22–1.57		1.0	0.38–1.59	0.49	1.0	0.48–1.87	0.87
	>55	0.58		0.28	0.78			0.94		
Karnofsky performance status	*>90*	1.0	0.55–4.20		1.0	0.75–3.53	0.22	1.0	0.84–3.70	0.13
	≤90	1.52		0.42	1.63			1.77		
Time interval from primary tumor to LR	*≥24 months*	1.0	1.12–9.09		1.0	1.32–8.33		1.0	1.27–7.69	
	<24 months	3.23		**0.03**	4.97		**0.01**	4.17		**0.01**
Macroscopic surgical specimen										
Primary site	*Endometrial*	1.0			1.0			1.0		
	Uterine cervix	1.64	0.51–5.26	0.41	3.98	0.43–32.81	0.22	1.35	0.64–2.86	0.43
	Ovarian	0.75	0.14–4.16	0.75	2.83	0.36–22.19	0.32	0.55	0.19–1.57	0.26
Recurrence site	*Pelvic*	1.0	0.20–1.88		1.0	1.0–4.25		1.0	0.76–3.05	0.23
	Paraaortic	0.60		0.38	2.07		**0.05**	1.52		
Recurrent tumor tumor size	*>5 cm*	1.0	0.41–3.97		1.0	0.68–4.66	0.24	1.0	0.74–4.34	0.22
	≤5 cm	1.28		0.67	1.78			1.79		
Tumor multifragmentation involvement	*Yes*	1.0	0.04–0.71		1.0	0.21–1.34	0.15	1.0	0.31–1.27	0.20
	No	0.16		**0.02**	0.67			0.63		
Microscopic surgical specimen										
Primary tumor histologic grade	*I–II*	1.0	0.64–4.67		1.0	1.15–4.88		1.0	1.18–4.87	0.10
	III	1.73		0.28	2.37		**0.02**	1.78		
Histologic subtype	*Adenocarcinoma*	1.0	1.13–8.57		1.0	0.74–3.32	0.25	1.0	0.72–3.17	0.23
	Squamous cell	3.11		**0.03**	1.56			1.52		
Recurrent tumor margin status	*R0*	1.0	0.76–5.76		1.0	0.68–2.88		1.0	0.68–2.16	0.41
	R1	2.09		0.15	1.37		0.36	1.33		
Recurrent tumor lymph node	*Positive*	1.0	0.26–2.20		1.0	0.62–3.09	0.32	1.0	0.77–3.0	0.23
	Negative	0.76		0.62	1.45			1.52		
Surgery										
Multiorgan resection	*Yes*	1.0	0.30–2.15		1.0	0.25–1.26	0.16	1.0	0.37–1.56	0.45
	No	0.80		0.66	0.56			0.76		
Vascular resection	*Yes*	1.0	0.06–1.26		1.0	0.13–2.38	0.43	1.0	0.15–2.69	0.54
	No	0.28		0.10	0.56			0.64		
Bone resection	*Yes*	1.0	0.04–2.0		1.0	0.23–1.90	0.44	1.0	0.22–1.79	0.38
	No	0.27		0.20	0.66			0.62		
Soft tissue resection	*Yes*	1.0	0.12–1.17		1.0	0.46–1.97	0.90	1.0	0.47–1.83	0.83
	No	0.38		0.09	0.95			0.93		

Tab. 3 Univariate analyses of associations between the patient, tumor, treatment, and pathologic characteristics and survival (Continued)

Parameter	Variable	Locoregional control			Disease-free survival			Overall survival		
		HR	CI 95%	p value	HR	CI 95%	p value	HR	CI 95%	p value
Treatment										
Primary tumor surgical treatment	*Yes*	1.0	0.66–8.73		1.0	0.56–3.03	0.55	1.0	0.71–7.15	0.20
	No	2.89		0.26	1.30			2.34		
Primary tumor RT treatment	*Yes*	1.0	0.34–2.82		1.0	0.85–3.79		1.0	0.85–3.56	0.13
	No	0.96		0.96	1.80		0.13	1.73		
Primary tumor adjuvant CT	*Yes*	1.0	0.28–1.98		1.0	0.39–1.64		1.0	0.38–1.48	0.40
	No	0.74		0.55	0.80		0.54	0.75		
Recurrent tumor RT treatment	*Yes*	1.0	1.62–20.24		1.0	1.01–3.99		1.0	1.18–4.87	
	No	5.73		**0.007**	1.90		**0.05**	2.39		**0.02**
Recurrent tumor adjuvant CT	*Yes*	1.0	0.26–2.56		1.0	0.22–1.67		1.0	0.31–1.86	0.54
	No	0.81		0.72	0.60		0.32	0.76		
IOERT dose	**≥12.5 Gy**	1.0	0.69–6.68		1.0	0.78–4.45		1.0	0.78–5.20	0.21
	<12.5 Gy	2.15		0.18	1.77		0.18	1.87		
IOERT fields	**1**	1.0	0.58–7,18		1.0	0.52–2.57	0.72	1.0	0.55–2.74	0.62
	2	2.04		0.27	1.16			1.22		

Tab. 4 Factors associated with locoregional control, distant metastases-free survival, disease-free survival and overall survival in multivariate analyses

Parameter	Variable	Locoregional control			Disease free survival			Overall survival		
		HR	CI 95%	p value	HR	CI 95%	p value	HR	CI 95%	p value
Recurrence site	*Pelvic*	–	–	–	1.0	1.10–4.38		–	–	–
	Paraaortic				2.27		**0.04**			
Time interval from primary tumor to LR	*≥24 months*	1.0			–	–	–	1.0		
	<24 months	4.02	1.20–14.29	**0.02**				2.32	1.16–4.76	**0.02**
Tumor fragmentation	*Yes*	1.0	0.17–0.88	**0.03**	–	–	–	–	–	–
	No	0.22								
Recurrent tumor RT treatment	*Yes*	1.0	1.21–10.92	**0.02**	1.0	1.11–6.32	**0.04**	1.0		
	No	3.95			3.52			3.77	1.08–8.87	**0.04**

(p=0.02) (**Tab. 3**). We found no difference in the LRR rate among patients with R0 resection and R1 resection (HR 1.65, p=0.15). After adjustment for other covariates, time interval from primary diagnosis to LR <24 months, not receiving EBRT to the LR, and no tumor fragmentation showed a significant association with LRC (**Tab. 4**). We then evaluated patients with and without radical surgery separately. For the subset with R0 resection (n=32), patients without tumor multifragment involvement experienced a significantly lower risk of local relapse in univariate analysis (HR 0.13, CI95% 0.01–0.96; p=0.05). Alternatively, for the subset with R1 resection (n=29), univariate analysis did not show that patients without tumor fragmentation had a decreased risk for a second local relapse (HR 0.28, CI95% 0.04–2.25; p=0.23). For the subset with R0 resection (n=32), patients who did not receive EBRT experienced a significantly higher risk of local relapse in univariate analysis (HR 7.69, CI95%1.0–56.9; p=0.05). Alternatively, for the subset with R1 resection (n=16), univariate analysis did not show that patients not receiving EBRT had an increased risk for a second local relapse (HR 3.59, CI95% 0.75–17.1; p=0.14). When tumor fragmentation was evaluated in patients with and without EBRT to the pelvic LRR, we found that only for the subset with tumor fragmentation (n=21), not receiving EBRT showed worse LRC [HR 4.20 (CI95% 1.16–15.23); p=0.03]. For patients without tumor fragmentation (n=14), this analysis did not reach statistical significance (HR 3.22, CI95% 0.51–9.23; p=0.25).

Causes of acute and chronic toxicity were estimated as multifactorial [17].

Tab. 5 Locally recurrent gynecological cancer results in IORT expert institutional experiences

	Median follow up	Primary advanced/locally recurrent	Pelvic recurrence/paraaortic recurrence	IORT dose [median]	EBRT [median dose]	5-year LC	5-year OS
IOERT							
Mayo Clinic Rochester Garton et al.[j] [4] (n=39)	25 (6.3–125.4)	3 (8%)/36 (92%)	25 (64%)/14 (36%)	17.5 Gy (10–25)	28 (72%) [45 Gy (0.9–65.7 Gy)]	67%	32%
Mayo Clinic Rochester Dowdy et al.[l] [12] (n=25)	NR	0/25 (100%)	19 (76%)/6 (24%)	15 Gy (10–25)	21 (84%) [48.6 Gy (9.0–50.7 Gy)]	76%	47%
Mayo Clinic Rochester Barney et al.[a,e,h] [11] (n=16)	44 (11–203)	3 (19%)/13 (81%)	16 (100%)/0	12.5 Gy (10–20)	16 (100%) [50.4 Gy (20–62.5 Gy)]	93%	53%
Mayo Clinic Rochester Haddock et al. [13] (n=148)	NR	23 (16%)/125 (84%)	NR	Unirradiated 20 Gy Reirradiated 15 Gy	113 (76%) [48.6 Gy (0.9–75.4 Gy)]	60%	27%
Mayo Clinic Rochester Barney et al.[a,d] [19] (n=89)	32 (1–306)	15 (17%)/74 (83%)	74 (83%)/15 (17%)	15 Gy (6.25–25)	61 (69%) [45 Gy (19.8–83 Gy)]	54%	25%
University of Washington Stelzer et al.[d] [6] (n=22)	Minimum 15	0/22 (100%)	22 (100%)/0	22 Gy (14–27.8)	13 (59%) [45 Gy (26–62.4 Gy)]	48%	43%
French IORT group Mahé et al.[d,f] [9] (n=70)	15 (2–69)	0/70 (100%)	70 (100%)/0	18 Gy (10–25)	30 (43%) [NR (20–45 Gy)]	21%	8%
University of Navarra Martínez-Monge et al.[db] [7] (n=67)	18.9 (1–138)	31 (46%)/36 (54%)	61 (91%)/6 (9%)	15 Gy (10–20)	35 (52%) [45 Gy (NR)]	42%	14%
Present series n=61	42 (2–169)	0/61 (100%)	35 (57%)/26 (43%)	12.5 Gy (10–15)	16 (46%) [45 Gy (30.6–50.4 Gy)]	65%	42%
Orthovoltage-IORT							
Stanford Tran et al.[f,g,h,i] [10] (n=36)	50 (2–198)	4 (11%)/32 (89%)	24 (67%)/12 (33%)	11.5 Gy (6–17.5)	19 (53%) [44 Gy (10–79)	45%	46%
HDR-IORT							
MSKCC Gemignani et al.[a] [5] (n=17)	20 (3–65)	0/17 (100%)	16 (94%)/3 (6%)	14 Gy (12–15)	2 (12%) [NR]	67%	54%
MSKCC Aubey et al.[k] [18] (n=56)	11.4 (NR)	0/56 (100%)	NR	14 Gy (12–15)	NR	NR	R0–R1: 60% R2: 20%

NR not reported, *OS* overall survival, *LC* local control. [a]3-year survival rates. [b]10-year survival rates. [c]Exclusive pelvic recurrence without synchronous para aortic recurrence. [d]Only uterine cervix patients. [e]Only uterine sarcoma. [f]Mean values. [g]No information regarding topography of perivascular-nodal relapse. [h]Follow up value for survivors. [i]Cancer specific survival. [j]6 patients relapsed in the pelvis and paraaortic region. [k]2-year survival rates. [l]Crude rates.

Overall 23 patients (38%) had grade ≥3 acute toxicity and 12 patients (20%) developed chronic toxicity ≥3 (Tab. 1). Overall treatment mortality was 2.9% (n=1, wound infection-sepsis). No long-term treatment related death occurred. In relation to perioperative mortality no difference was found [3% (n=1) vs. 0% (n=0); p=0.65] between patients treated for pelvic and paraaortic recurrence site.

Discussion

Our most relevant findings can be summarized as follows. First, we observed that not adding EBRT to surgery and IOERT

to patients with ORGC was significantly associated with an increased probability of LRR, overall metastases, and death (**Fig. 1d, e, f**). Interestingly, this association maintained significance with regard to LRR when patients with tumor fragmentation and R0 resection were analyzed separately. Second, patients with paraaortic LR had an increased risk of overall metastases when compared to patients with pelvic LR. Third, we found that patients with a time interval <24 months between primary tumor diagnosis and LR had an increased probability of LR and death. Finally, patients without tumor fragmentation had a decreased probability of LRR.

Oligometastasis implies a restricted locoregional tumor burden and has been proposed as a status candidate for intense treatment strategies combining surgery, radiotherapy, and chemotherapy [1]. Oligotopic cancer has become synonymous with isolated metastases arising from micrometastases that have been dormant for variable periods of time [1]. Several IORT-expert institutions have analyzed mixed cohorts with broad inclusion criteria and reported results comparable to this retrospective single center study (**Tab. 5**). The present analysis had no selection as to primary site, modalities of initial treatment, volume of tumor recurrence, and included patients with pelvic and paraaortic ORGC. Discrimination between ORGC and primary advanced tumors is important because survival (10-year OS 14 vs. 67%; p<0.001) and local control (10-year IOERT in field control 47 vs. 93%; p<0.001) of patients treated for primary advanced disease has been reported to be superior [7].

Improved survival and LRC has been frequently reported to be associated to the achievement of a gross total resection (R0/R1 resection) prior to IORT [7, 13]. In an updated Mayo Clinic data reported by Haddock et al. [13], 148 patients (84% ORCG) with gynecological tumors were treated with maximal surgical resection plus IOERT (76% EBRT). The 5-year LRC and OS was 60 and 27% for the total group. Patients with an R2 resection had a significantly lower survival than patients with R0/R1 resection (5-year OS 13 vs. 31%; p=0.01). The distant metastases rate was decreased in patients with R0/R1 vs. R2 resection (5-year 49 vs. 58%), but LRC at 5-years was 74% for patients with R2 resection versus 58% for patients with R0/R1 resection. The high LRC in R2 patients may be explained to the increased rate of distant metastases and subsequent death before local relapse was clinically evident.

Aubey et al. [18] reported 56 patients with ORGC that were treated with radical resection followed by HDR-IORT. With a median follow-up of 11.4 months, 2-year survival rate for patients with R2 resections was 20 compared to 60% for those with R0/R1 resections (p<0.01). A French multi-institutional analysis reported by Mahe et al. [9] observed no difference in the distant metastatic rate. However, because LRC rate in the R2 group was 16% it is likely that many of these patients died of uncontrolled local disease progression prior to distant metastases manifestation [9]. In the current series the use of an IOERT containing multimodality strategy has impacted the extent of surgical resection (no patient had gross residual disease); in regard to the extent of surgical resection (R0 vs. R1) we found no difference in LRC or OS. In the mentioned Mayo Clinic experience [13], a worse survival was reported for patients with a disease-free interval (DFI) ≤2 years compared to those with a DFI >2 years (5-year OS 14 vs. 35%; p=0.002). Our observation that patients with a DFI <24 months had worse overall outcomes than patients with a DFI ≥24 months is consistent with previously reported findings.

The clinical significance of including an EBRT-component in a multimodality IORT-containing treatment for ORGC is uncertain. Previously irradiated patients (with assumed radioresistant biology) has been associated to adverse and inferior results in reported, but this observation has not been confirmed in the current series or other expert institutional analysis [7, 13].

A combinatorial dose escalation strategy combining EBRT and IORT has not been consistently associated with improved outcomes. The Mayo Clinic series of 25 recurrent endometrial cancer patients [12] showed that EBRT was associated with improved survival (p=0.019). In the Mayo Clinic series of 89 patients with cervical cancer [locally recurrent (83%) or primary advanced (17%)] treated with IOERT following surgical resection (69% received perioperative EBRT) [19]. Pelvic exenteration and perioperative EBRT were associated with improved LRC on multivariate analysis. Consistently, with this finding we found that patients without EBRT treatment of the LR had inferior overall outcomes than patient treated with EBRT. Moreover, patients with tumor fragmentation and R0 resection treated without EBRT had worse LRC than those who did received EBRT treatment. However, the optimal treatment sequence together with the contribution of an external beam radiation therapy (EBRT) component in this clinical scenario remains to be elucidated.

It has been reported that patients with ORGC exclusively in the paraaortic region can achieve excellent LRC and survival with salvage therapy [20]. In the current analysis, although paraaortic isolated lymph node recurrence was associated with equivalent LRC and survival rates when compared to pelvic recurrence, an increased incidence of overall metastases was observed suggesting a superior migration potential.

The interpretation of treatment-related toxicity, tolerance, and rate of postsurgical complications suggests that a multimodality approach including an IORT component for ORGC is feasible with tolerable risks and not limited by prohibitive long-term side effects.

We acknowledge several limitations of our study. First, the population was heterogeneous, having been treated over 18 years and receiving different treatment combinations. Although we did observe an association between EBRT treatment and LRC after adjustment for several potential confounding factors, the presence of a selection bias for patients referred for radiation therapy to a higher dose cannot be completely dismissed. We certainly acknowledge that patients that did not consent to EBRT had greater concerns related to re-treatment toxicity or issues related to treatment efficacy. A systematic method of follow-up, including imaging, would be optimal to evaluate patterns of failure after radiation therapy [21, 22]. Given the retrospective nature of this analysis, consistent homogeneous imaging did not oc-

cur in a proportion of patients. Therefore, a significant number of patients with distant only recurrence may not have undergone optimal imaging of the pelvis at the time of recurrence. Finally, it must be emphasized that systemic therapy plays an important role in the management of ORGC (specially in patients with paraaortic lymph node metastases).

Conclusion

We found that ORGC patients that received EBRT and IOERT were safely treated and had improved rates of LRC. We also found that patients with tumor fragmentation and R0 resections experienced the largest benefit with EBRT treatment. A certain level of prognostic adversity (nonradical resections) might be compensated by the addition of EBRT. Our results suggest that a subgroup of patients with ORGC could benefit from intensive local treatment to the isolated local relapse.

Corresponding address

C.V. Sole, M.D.
Department of Oncology, Hospital General Universitario Gregorio Marañón
C/Doctor Esquerdo, 46, 28007 Madrid
Spain
cvsole@uc.cl

Acknolwedgments. Supported in part by a grant from the Health Institute of Research Carlos III, Spanish Ministry of Science and Innovation (project code PI11-02908), and by the Spanish Ministry of Economy and Competitiveness (TEC2010-21619-C04, IPT-300000-2010-003, IPT-2012-0401-300000).

Compliance with ethical guidelines

Conflict of interest. C.V. Sole, F.A. Calvo, M.A. Lozano, L. Gonzalez-Bayon, C. Gonzalez-Sansegundo, A. Alvarez, S. Lizarraga, and J.L. García-Sabrido state that there are no conflicts of interest.

All studies on humans described in the present manuscript were carried out with the approval of the responsible ethics committee and in accordance with national law and the Helsinki Declaration of 1975 (in its current, revised form). Informed consent was obtained from all patients included in studies.

References

1. Weichselbaum RR, Hellman S (2011) Oligometastases revisited. Nat Rev Clin Oncol 8:378–382
2. Hockel M, Dornhofer N (2006) Pelvic exenteration for gynaecological tumours: achievements and unanswered questions. Lancet Oncol 7:837–847
3. Perez CA, Kuske RR, Camel HM et al (1988) Analysis of pelvic tumor control and impact on survival in carcinoma of the uterine cervix treated with radiation therapy alone. Int J Radiat Oncol Biol Phys 14:613–621
4. Garton GR, Gunderson LL, Webb MJ et al (1997) Intraoperative radiation therapy in gynecologic cancer: update of the experience at a single institution. Int J Radiat Oncol Biol Phys 37:839–843
5. Gemignani ML, Alektiar KM, Leitao M et al (2001) Radical surgical resection and high-dose intraoperative radiation therapy (HDRIORT) in patients with recurrent gynecologic cancers. Int J Radiat Oncol Biol Phys 50:687–694
6. Stelzer KJ, Koh WJ, Greer BE et al (1995) The use of intraoperative radiation therapy in radical salvage for recurrent cervical cancer: outcome and toxicity. Am J Obstet Gynecol 172:1881–1888
7. Martínez-Monge R, Jurado M, Aristu JJ et al (2001) Intraoperative electron beam radiotherapy during radical surgery for locally advanced and recurrent cervical cancer. Gynecol Oncol 82:538–543
8. Carmen MG del, Eisner B, Willet CG et al (2003) Intraoperative radiation therapy in the management of gynecologic and genitourinary malignancies. Surg Oncol Clin N Am 12:1031–1042
9. Mahe MA, Gerard JP, Dubois JB et al (1996) Intraoperative radiation therapy in recurrent carcinoma of the uterine cervix: report of the French intraoperative group on 70 patients. Int J Radiat Oncol Biol Phys 34:21–26
10. Tran PT, Su Z, Hara W et al (2007) Long-term survivors using intraoperative radiotherapy for recurrent gynecologic malignancies. Int J Radiat Oncol Biol Phys 69:504–511
11. Barney BM, Petersen IA, Dowdy SC et al (2012) Long-term outcomes with intraoperative radiotherapy as a component of treatment for locally advanced or recurrent uterine sarcoma. Int J Radiat Oncol Biol Phys 83:191–197
12. Dowdy SC, Mariani A, Cliby WA et al (2006) Radical pelvic resection and intraoperative radiation therapy for recurrent endometrial cancer: technique and analysis of outcomes. Gynecol Oncol 101:280–286
13. Haddock MG, Martinez-Monge R, Petersen IA, Wilson TO (2011) Locally advanced primary and recurrent gynecological malignancies: EBRT with or without IOERT or HDR-IORT. In: Gunderson LL, Willett CG, Calvo FA, Harrison LB (eds) Intraoperative irradiation. Techniques and results, 2nd edn. Springer, New York
14. Pascau J, Santos Miranda JA, Calvo FA et al (2012) An innovative tool for intraoperative electron beam radiotherapy simulation and planning: description and initial evaluation by radiation oncologists. Int J Radiat Oncol Biol Phys 83:287–295
15. Clavien PA, Barkun J, Oliveira ML de et al (2009) The Clavien–Dindo classification of surgical complications: five-year experience. Ann Surg 250:187–196
16. Cox JD, Stetz J, Pajak TF (1995) Toxicity criteria of the Radiation Oncology Group (RTOG) and the European Organization for Research and Treatment of Cancer (EORTC). Int J Radiat Oncol Biol Phys 31:1341–1346
17. Azinovic I, Calvo FA, Puebla F et al (2001) Long-term normal tissue effects of intraoperative electron radiation therapy (IOERT): late sequelae, tumor recurrence, and second malignancies. Int J Radiat Oncol Biol Phys 49:597–604
18. Aubey JJ, McCreath W, Chi DS, Alektiar K et al (2004) Outcomes of patients with recurrent gynecological malignancues treated with with radical surgical resection and high-dose rate intraoperative radiotherapy (HDR-IORT). The 35th Annual SGO meeting in San Diego, CA
19. Barney BM, Petersen IA, Dowdy SC et al (2013) Intraoperative Electron Beam Radiation Therapy (IOERT) in the management of locally advanced or recurrent cervical cancer. Radiat Oncol 8:80 (Epub ahead of print)
20. Singh AK, Grigsby PW, Rader JS et al (2005) Cervix carcinoma, concurrent chemoradiotherapy, and salvage of isolated paraaortic lymph node recurrence. Int J Radiat Oncol Biol Phys 61:450–455
21. Brocker KA, Alt CD, Eichbaum M et al (2011) Imaging of female pelvic malignancies regarding MRI, CT, and PET/CT: part 1. Strahlenther Onkol 187:611–618
22. Alt CD, Brocker KA, Eichbaum M et al (2011) Imaging of female pelvic malignancies regarding MRI, CT, and PET/CT: part 2. Strahlenther Onkol 187:705–714

SPRINGER LICENSE
TERMS AND CONDITIONS

Dec 09, 2013

This is a License Agreement between Claudio V Sole ("You") and Springer ("Springer") provided by Copyright Clearance Center ("CCC"). The license consists of your order details, the terms and conditions provided by Springer, and the payment terms and conditions.

All payments must be made in full to CCC. For payment instructions, please see information listed at the bottom of this form.

License Number	3284860371048
License date	Dec 09, 2013
Licensed content publisher	Springer
Licensed content publication	Strahlentherapie und Onkologie
Licensed content title	External-beam radiation therapy after surgical resection and intraoperative electron-beam radiation therapy for oligorecurrent gynecological cancer
Licensed content author	C.V. Sole M.D.
Licensed content date	Jan 1, 2013
Type of Use	Thesis/Dissertation
Portion	Full text
Number of copies	10
Author of this Springer article	Yes and you are a contributor of the new work
Order reference number	
Title of your thesis / dissertation	Valor Pronóstico de la Radioterapia Externa en el Tratamiento Multidisciplinario de Pacientes con Oligorecurrencia Locoregional
Expected completion date	Dec 2014
Estimated size(pages)	120
Total	0.00 USD
Terms and Conditions	

Introduction
The publisher for this copyrighted material is Springer Science + Business Media. By clicking "accept" in connection with completing this licensing transaction, you agree that the following terms and conditions apply to this transaction (along with the Billing and Payment terms and conditions established by Copyright Clearance Center, Inc. ("CCC"), at the time that you opened your Rightslink account and that are available at any time at http://myaccount.copyright.com).

Limited License
With reference to your request to reprint in your thesis material on which Springer Science and Business Media control the copyright, permission is granted, free of charge, for the use indicated in your enquiry.

Licenses are for one-time use only with a maximum distribution equal to the number that

No Transfer of License
This license is personal to you and may not be sublicensed, assigned, or transferred by you to any other person without Springer Science + Business Media's written permission.

No Amendment Except in Writing
This license may not be amended except in a writing signed by both parties (or, in the case of Springer Science + Business Media, by CCC on Springer Science + Business Media's behalf).

Objection to Contrary Terms
Springer Science + Business Media hereby objects to any terms contained in any purchase order, acknowledgment, check endorsement or other writing prepared by you, which terms are inconsistent with these terms and conditions or CCC's Billing and Payment terms and conditions. These terms and conditions, together with CCC's Billing and Payment terms and conditions (which are incorporated herein), comprise the entire agreement between you and Springer Science + Business Media (and CCC) concerning this licensing transaction. In the event of any conflict between your obligations established by these terms and conditions and those established by CCC's Billing and Payment terms and conditions, these terms and conditions shall control.

Jurisdiction
All disputes that may arise in connection with this present License, or the breach thereof, shall be settled exclusively by arbitration, to be held in The Netherlands, in accordance with Dutch law, and to be conducted under the Rules of the 'Netherlands Arbitrage Instituut' (Netherlands Institute of Arbitration).***OR:***

All disputes that may arise in connection with this present License, or the breach thereof, shall be settled exclusively by arbitration, to be held in the Federal Republic of Germany, in accordance with German law.

Other terms and conditions:

v1.3

If you would like to pay for this license now, please remit this license along with your payment made payable to "COPYRIGHT CLEARANCE CENTER" otherwise you will be invoiced within 48 hours of the license date. Payment should be in the form of a check or money order referencing your account number and this invoice number RLNK501177970.
Once you receive your invoice for this order, you may pay your invoice by credit card. Please follow instructions provided at that time.

Make Payment To:
Copyright Clearance Center
Dept 001
P.O. Box 843006
Boston, MA 02284-3006

For suggestions or comments regarding this order, contact RightsLink Customer Support: customercare@copyright.com or +1-877-622-5543 (toll free in the US) or +1-978-646-2777.

Gratis licenses (referencing $0 in the Total field) are free. Please retain this printable license for your reference. No payment is required.

International Journal of
Radiation Oncology
biology • physics

www.redjournal.org

Clinical Investigation: Sarcoma

Prognostic Value of External Beam Radiation Therapy in Patients Treated With Surgical Resection and Intraoperative Electron Beam Radiation Therapy for Locally Recurrent Soft Tissue Sarcoma: A Multicentric Long-Term Outcome Analysis

Felipe A. Calvo, MD, PhD,[*,†] Claudio V. Sole, MD,[*,†,‡] Mauricio Cambeiro, MD, PhD,[§] Angel Montero, MD,[||] Alfredo Polo, MD, PhD,[||] Carmen Gonzalez, MD,[†,‡,§,||,¶] Miguel Cuervo, MD,[#] Mikel San Julian, MD,[**] Jose L. Garcia-Sabrido, MD, PhD,[†,††] and Rafael Martinez-Monge, MD, PhD[§]

Department of Oncology, Hospital General Universitario Gregorio Marañón, Madrid, Spain; [†]School of Medicine, Complutense University, Madrid, Spain; [‡]Service of Radiation Oncology, Instituto de Radiomedicina, Santiago, Chile; [§]Service of Radiation Oncology, Clínica Universitaria, Universidad de Navarra, Pamplona, Spain; [||]Service of Radiation Oncology, Hospital Universitario Ramón y Cajal, Universidad de Alcala, Madrid, Spain; [¶]Service of Radiation Oncology, Hospital General Universitario Gregorio Marañón, Madrid, Spain; [#]Service of Orthopedics and Traumatology, Hospital General Universitario Gregorio Marañón, Madrid, Spain; [**]Service of Orthopedics and Traumatology, Clínica Universitaria, Universidad de Navarra, Pamplona, Spain; and [††]Service of General Surgery III, Hospital General Universitario Gregorio Marañón, Madrid, Spain

Received Jul 8, 2013, and in revised form Sep 2, 2013. Accepted for publication Oct 15, 2013.

Summary

Recognition of the high risk of local recurrence and death from locally recurrent soft tissue sarcomas has led to interest in the use of radical intent surgical resection, external beam radiation

Background: A joint analysis of data from centers involved in the Spanish Cooperative Initiative for Intraoperative Electron Radiotherapy was performed to investigate long-term outcomes of locally recurrent soft tissue sarcoma (LR-STS) patients treated with a multidisciplinary approach.

Methods and Materials: Patients with a histologic diagnosis of LR-STS (extremity, 43%; trunk wall, 24%; retroperitoneum, 33%) and no distant metastases who underwent radical surgery and intraoperative electron radiation therapy (IOERT; median dose, 12.5 Gy) were considered eligible for participation in this study. In addition, 62% received external beam radiation therapy (EBRT; median dose, 50 Gy).

Reprint requests to: Claudio V. Sole, MD, Hospital General Universitario Gregorio Marañon, C/ Doctor Esquerdo, 46-28007 Madrid, Spain. Tel: (34) 91 586 85 99; E-mail: cvsole@uc.cl

Supported in part by a grant from the Health Institute of Research Carlos III, Spanish Ministry of Science and Innovation (project code PI11-02908) and Heath Research Institute Gregorio Marañon, Madrid, Spain.

Conflict of interest: none.

Acknowledgments—The authors express their gratitude to all the health care professionals involved in intraoperative electron beam radiation therapy (IOERT) programs during the time period analyzed, and in particular, to the pioneering senior surgeons involved: Prof. Jose Cañadell (University Clinic of Navarra) and Prof. Miguel Ferrer (Hospital General Universitario Gregorio Marañon).

Int J Radiation Oncol Biol Phys, Vol. 88, No. 1, pp. 143–150, 2014
0360-3016/$ - see front matter
http://dx.doi.org/10.1016/j.ijrobp.2013.10.021

therapy, and intraoperative electron radiation therapy (IOERT). These mature data add further evidence that an intensified radiation and surgical treatment promotes loco-regional control, compensating for some adverse disease features in the context of an advanced multimodality rescue strategy.

Results: From 1986 to 2012, a total of 103 patients from 3 Spanish expert IOERT institutions were analyzed. With a median follow-up of 57 months (range, 2-311 months), 5-year local control (LC) was 60%. The 5-year IORT in-field control, disease-free survival (DFS), and overall survival were 73%, 43%, and 52%, respectively. In the multivariate analysis, no EBRT to treat the LR-STS ($P=.02$) and microscopically involved margin resection status ($P=.04$) retained significance in relation to LC. With regard to IORT in-field control, only not delivering EBRT to the LR-STS retained significance in the multivariate analysis ($P=.03$).

Conclusion: This joint analysis revealed that surgical margin and EBRT affect LC but that, given the high risk of distant metastases, DFS remains modest. Intensified local treatment needs to be further tested in the context of more efficient concurrent, neoadjuvant, and adjuvant systemic therapy. © 2014 Elsevier Inc.

Introduction

Soft tissue sarcomas (STS) are uncommon tumors with heterogenous biological properties and histologic findings (1). Complete resection is the primary therapy for most STS in adults, but patients with locally recurrent STS (LR-STS) have poor local control and survival (2). Clinical practice has shifted from nonintervention or palliative treatment to more intensive multimodal approaches, with radical rescue surgery providing local control in approximately half of all patients (3, 4). The success of rescue treatment is highly dependent on the extent of local extension, invasion, fixation, and radicality of resection (2-4). A completely negative resection margin is often difficult to achieve owing to close proximity to or proven invasion of adjacent postresection tumor bed areas, or unresectable structures. Therefore, multimodal approaches including additional local therapies should be implemented to further improve patient outcomes and to optimize local control and survival (5). Few studies have specifically analyzed the prognosis of patients with LR-STS involving the extremities, trunk wall, and retroperitoneum (6-13). We performed a joint study of data from the Spanish Cooperative Initiative for Intraoperative Electron Radiotherapy to analyze long-term outcomes and novel risk factors for a group of patients with LR-STS treated with radical surgery and intraoperative electron beam radiation therapy (IOERT) in high-risk areas (postresection and prereconstruction), with and without external-beam radiation therapy (EBRT).

Methods and Materials

Patient characteristics and staging evaluation

This study was approved by our institutional review board and performed in compliance with local ethical and clinical practice guidelines. The study population comprised adult patients (>18 years) with pathologically confirmed nonmetastatic LR-STS and curative resections with either close (<1 cm) or positive margins. The tumor board recommended a multimodal approach after taking into account initial treatment characteristics, location, resectability, and clinical status. All patients (n=103) were invited to participate in a developmental protocol that consisted of rescue surgery, EBRT, and IOERT delivered to the area of the tumor bed that was at risk for residual disease EBRT plus IOERT program, but 40 patients (39%) elected not to consent the EBRT component (patients who did not consent EBRT had greater concerns related to retreatment toxicity or issues related to treatment efficacy). Two treatment strategies were operational along the period: 63 patients (61%) were treated according to a research protocol that consisted of EBRT, surgery, and IOERT with or without adjuvant chemotherapy (EBRT group). The remaining 40 patients were treated with surgery plus IOERT, but without EBRT (non-EBRT group) and served as the control cohort. The surgical approach and adjuvant chemotherapy were discussed on an individual basis. Prospectively collected hospital records of 103 patients registered in the IOERT program and treated for LR-STS between June 1986 and April 2012 were retrospectively reviewed at the time of scheduled follow-up. Pretreatment evaluation consisted of a complete history and physical examination, complete blood count, renal and liver function tests, chest x-ray, and computed tomography (CT) or magnetic resonance imaging (MRI) of the tumor site, chest, and abdomen. Patients were reclassified according to the seventh American Joint Committee on Cancer (AJCC)/International Union Against Cancer (UICC) staging system. Patient and treatment characteristics are listed in Table 1. No significant differences in baseline variables were detected between patients treated with or without EBRT.

Treatment characteristics

EBRT and concomitant and adjuvant chemotherapy were administered following standards described elsewhere (5). Conformal 3-dimensional postoperative EBRT (n=63, 62%) was delivered with megavoltage equipment (6-15 MV). Fields were arranged taking into account doses delivered to normal tissues during radiation therapy for the primary tumor. However, no specific dose−volume constraints were indicated in the treatment protocol. Non-irradiated patients (n=46) received a total median dose of 50 Gy (range, 45-50.4 Gy [1.8-2.0 Gy/5 days/wk]) and re-irradiated patients (n=17) received 30.6 Gy (range, 21.6-30.6 Gy [1.8 Gy/5 days/wk]), both of which were prescribed to the isodose line that covered the planning target volume (PTV) to obtain a homogeneity of ±5% of the prescribed dose according to the International Commission on Radiation Units and Measurements Report No. 50. The technique for the EBRT component consisted of conventional (2D-RT) EBRT for patients treated between 1986 and 1992 (n=12, 20%), and conformal (3D-CRT) EBRT for patients treated after 1992 (n=49, 80%). PTV for 2D-RT was defined as tumor bed plus 3 cm in the radial directions in all cases, and for the longitudinal directions a 5-cm margin was applied for extremity LR-STS and a 3-cm margin was added for trunk wall and retroperitoneal LR-STS (the field could be shortened to include

Table 1 Patient, tumor, and treatment characteristics

Parameter	Variable	All patients n = 103 (%)	EBRT group n = 63 (61%)	No-EBRT group n = 40 (39%)	*P* value
Patient variables					
Age	Median age (y)	53 (23-78)	54 (31-78)	52 (33-76)	.89
Sex	Male	40 (39)	26 (41)	14 (35)	.71
	Female	63 (61)	37 (59)	16 (65)	
Karnofsky perfomance status	<90	27 (26)	15 (24)	12 (30)	.55
	≥90	76 (74)	48 (76)	28 (70)	
Time interval from primary to LR (mo)	≥24	54 (53)	32 (51)	22 (55)	.68
	<24	49 (47)	31 (49)	20 (45)	
Presurgical variables					
Tumor size	Median tumor size (cm)	9 (2-24)	9 (3-24)	10 (3-20)	.78
Tumor localization	Extremity	44 (43)	32 (51)	12 (30)	.19
	Retroperitoneum	34 (33)	18 (28)	16 (40)	
	Trunk wall	25 (24)	13 (21)	12 (30)	
Tumor depth	Deep	79 (77)	46 (73)	33 (83)	.46
	Superficial	24 (23)	17 (27)	7 (17)	
Microscopic surgical specimen					
Histologyc subtype	Liposarcoma	38 (37)	21 (33)	17 (43)	.53
	Malignant fibrous histiocytoma	19 (18)	14 (22)	5 (13)	
	Leiomyosarcoma	11 (11)	5 (8)	6 (10)	
	Sarcoma NOS	8 (8)	6 (10)	2 (3)	
	Synovial sarcoma	8 (8)	7 (11)	1 (2)	
	Other	19 (18)	10 (16)	9 (14)	
Mitosis count	Low-medium	83 (81)	49 (78)	34 (85)	.44
	High	20 (19)	14 (22)	6 (15)	
Necrosis	Yes	44 (43)	24 (39)	20 (50)	.60
	No	59 (57)	39 (61)	20 (50)	
Histologic grade	1-2	73 (71)	46 (63)	27 (68)	.82
	3	30 (29)	17 (37)	13 (32)	
Surgery					
Surgical procedure	Wide excision	64 (62)	40 (63)	24 (60)	.78
	Simple local excision	39 (38)	23 (37)	16 (40)	
Margin status	R0	62 (60)	37 (59)	25 (63)	.68
	R1	41 (40)	26 (41)	15 (37)	
IOERT technical parameters					
IOERT dose (cGy)	Median IOERT dose (cGy)	1250 (1000-2000)	1200 (1000-2000)	1250 (1000-2000)	.89
IOERT energy (MeV)	Median IOERT energy (MeV)	9 (4-20)	8 (4-20)	9 (4-18)	.54
IOERT applicator size (cm)	Median IOERT applicator size (cm)	9 (5-15)	9 (5-15)	10 (5-15)	.65
EBRT-CT treatment					
Adjuvant CT	Yes	36 (35)	19 (30)	17 (41)	.28
	No	67 (65)	44 (70)	23 (58)	
EBRT to the primary tumor	Yes	31 (30)	17 (27)	14 (35)	.21
	No	72 (70)	46 (73)	26 (65)	

Abbreviations: CT = chemotherapy; EBRT = external beam radiation therapy; IOERT = intraoperative electron beam radiation therapy; NOS = not otherwise specified.

the end of the compartment). Clinical target volume (CTV) for the 3D-CRT technique included the surgical tumor bed plus a 2-cm margin in the radial directions. A 3-cm margin in the longitudinal (proximal and distal) directions was used in the case of extremity locations, and for trunk wall and retroperitoneal LR-STS, a 2-cm margin was used. PTV was defined as CTV plus a 1 cm margin in longitudinal and radial directions. The surgical approach (4-6 weeks before EBRT treatment) consisted of wide resection (62%) or marginal resection (38%). Patients with a higher histologic grade (grade 3) and tumor size (≥5 cm) were offered adjuvant chemotherapy (most commonly 4 or 5 cycles of doxorubicin 75 mg/m^2 and ifosfamide 5 g/m^2 every 3 weeks). The IOERT program was performed in a nondedicated linear accelerator under an outpatient regimen. After resection and before reconstruction, 10 to 20 Gy (median, 12.5 Gy) were delivered in a single fraction to 1-field PTVs (n = 75, 73%) or 2-field PTVs (n = 28, 27%) using a median energy of 9 MeV (range, 4-20 MeV) (Table 2). The dose was delivered to the 90% isodose line covering the surgical bed. The IOERT dose was chosen according to the EBRT dose, margins (intraoperative margin status was assessed using frozen pathologic sections) and surgical bed volumes. Beveled (15°-45°) Lucite circular applicators (size range, 5-15 cm) were adjusted to collimate the target surface air gap, thus allowing dosimetric adaptation and uniform dose distribution. IOERT CT-guided treatment has been available since 2008 (14).

Table 2 Correlations between macroscopic/microscopic pathology characteristics and intraoperative electron beam radiation therapy (IOERT) technical parameters

	Applicator size	IOERT dose (Gy)	IORT energy (MeV)
Pathology/IOERT treatment	Median/ range	Median/ range	Median/ range
Tmax size (cm)			
2.0-3.0	6/5-8	12.5/10-20	8/4-20
3.1-6.0	9/5-9	12.5/12.5-20	8/4-20
6.1-10.0	9/6-10	12.5/10-15	9/6-20
10.1-15.0	9/7-15	12.5/12.5-15	9/4-20
15.1-24.0	9/9-15	12.5/10-15	9/6-20
Margin resection status			
R0	9/5-15	12.5/10-20	9/4-20
R1	9/5-15	12.5/12.5-20	9/6-20

Abbreviation: Tmax = tumor maximal dimension.
Multiple field technique procedures in 28 (27%) patients.

Follow-up and toxicity evaluation

All patients were followed up according to a common protocol every 3 months after completion of treatment for the first 3 years and every 6 months for an additional 3 years thereafter. Patients were restaged 4 weeks after EBRT and routinely every 6 months with chest x-ray and CT or MRI of the initial tumor site.

Acute and late toxicities were evaluated according to the criteria of the Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer (15).

Statistical analysis

Data were analyzed using SPSS (version 19.0). The primary endpoint of the analysis was local control (freedom from EBRT in-field progression). Secondary endpoints were IOERT in-field control (freedom from IOERT in-field progression), disease-free survival (DFS), and overall survival (OS). Potential associations for survival outcomes were assessed in the univariate and multivariate analyses using the Cox proportional hazards model. Based on P values $\leq$.10 in the univariate analysis and clinical relevance, multivariate analysis was performed using a stepwise regression model to identify variables that have an effect on survival outcomes ($P \leq .05$, 2-sided).

Results

Median follow-up time for all patients was 57 months (range, 2-311 months). A total of 41 patients remained alive at the time of the analysis. The median follow-up for surviving patients was 80 months (range, 4-311 months). Of the 62 deceased patients, 55 (89%) died of progression of sarcoma, and 7 (11%) died of causes unrelated to their sarcomas or treatment. The crude local relapse rate was 34% (n = 35); 36% of the patients (n = 37) developed distant metastases (most commonly pulmonary [n = 18, 49%]). Of the 35 patients who had local progression, 18 (51%, crude rate) underwent a new surgical procedure for rescue [median time to surgical rescue 23.3 months (range, 6.7-61.4 months)], with long-term local sarcoma control in 11 patients (61%, crude rate). The remaining 17 patients had synchronous distant metastases with local relapse and received chemotherapy alone (n = 82%) or no further therapy (n = 18%).

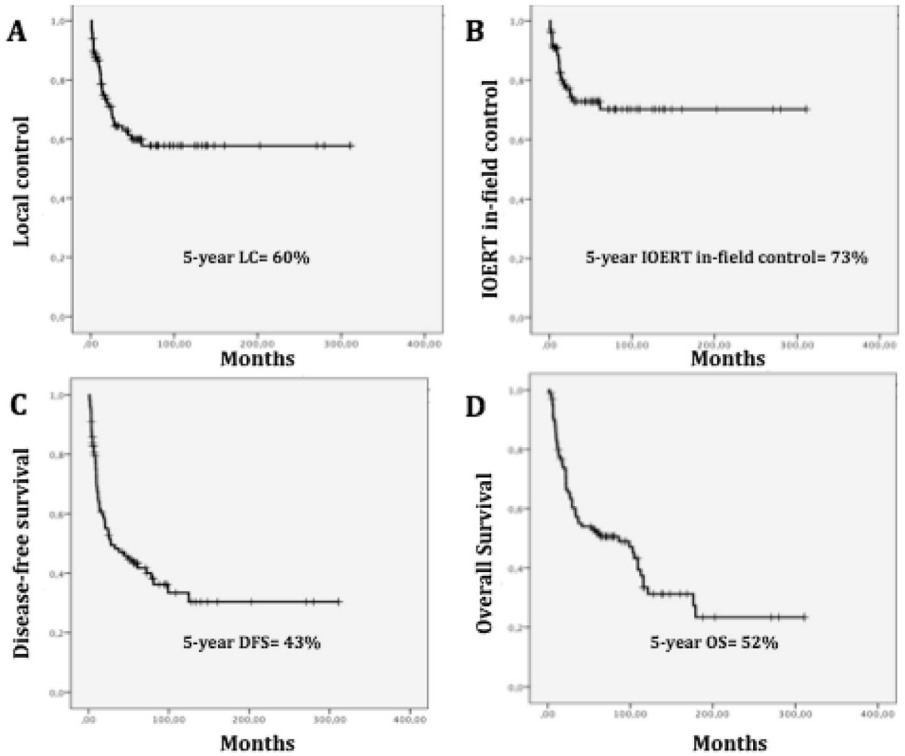


Fig. 1. Kaplan-Meier curves for all 68 patients: local control (A), IOERT in-field control (B), disease-free survival (C), and overall survival (D).

Table 3 Univariate analyses of associations between the patient, tumor, and treatment with local control, intraoperative electron beam radiation therapy (IOERT) in-field control, disease-free survival, and overall survival

		Local control			IOERT in-field control			Disease-free survival			Overall survival		
Parameter	Variable	HR	95% CI	*P* value	HR	95% CI	*P* value	HR	95% CI	*P* value	HR	95% CI	*P* value
Patient variables													
Sex	Male	1.0			1.0			1.0			1.0		
	Female	0.98	0.50-1.91	.95	0.80	0.39-1.64	.54	0.80	0.47-1.36	.41	0.87	0.33-1.53	.45
Age (y)	<50	1.0			1.0			1.0			1.0		
	≥50	1.09	0.54-2.20	.81	0.82	0.34-1.97	.65	1.33	0.76-2.33	.32	1.59	1.02-2.32	.05
Karnofsky perfomance status	<90	1.0			1.0			1.0			1.0		
	≥90	0.61	0.28-1.51	.34	0.78	0.34-2.04	.45	0.84	0.35-2.10	.67	0.88	0.20-2.16	.71
Time interval from primary to LR (mo)	≥24	1.0			1.0			1.0			1.0		
	<24	2.47	1.03-5.19	.04	2.95	0.73-7.61	.17	3.65	1.21-7.23	.01	3.18	1.25-6.88	.01
Presurgical variables													
Tumor size (cm)	≤10	1.0			1.0		.67	1.0			1.0		
	>10	1.64	0.91-2.94	.10	1.17	0.58-2.32		1.14	0.869-1.88	.60	1.22	0.74-2.23	.31
Tumor localization	Extremity	1.0			1.0			1.0			1.0		
	Retroperitoneal	2.26	0.85-4.64	.14	2.33	0.78-6.09	.27	1.75	0.83-3.49	.19	1.35	0.74-2.50	.33
	Trunk wall	1.59	0.71-3.10	.31	1.33	0.55-3.18	.53	1.61	0.79-3.08	.23	1.30	0.73-2.33	.38
Tumor depth	Superficial	1.0			1.0			1.0			1.0		
	Deep	1.91	0.74-4.11	.22	2.98	0.37-8.75	.35	1.21	0.43-3.82	.41	1.24	0.37-3.91	.86
Microscopic surgical specimen													
Histologic subtype	Liposarcoma	1.0			1.0		.88	1.0			1.0		
	Others	1.24	0.68-2.56	.49	1.05	0.53-2.08		1.53	0.90-2.55	.13	1.31	0.77-2.23	.32
Mitosis count	Low-medium	1.0			1.0		.16	1.0			1.0		
	High	2.14	0.95-4.81	.07	1.95	0.78-4.94		1.60	0.91-2.68	.13	1.39	0.66-2.89	.39
Necrosis	Yes	1.0			1.0		.88	1.0			1.0		
	No	0.75	0.26-2.41	.35	1.12	0.54-2.61		0.51	0.21-1.25	.23	0.65	0.31-1.19	.17
Histologic grade	1-2	1.0			1.0		.23	1.0			1.0		
	3	1.86	1.02-3.43	.05	1.55	0.76-3.18		2.26	1.17-4.36	.02	1.64	0.96-2.79	.07
Surgery													
Resection	Wide resecrion	1.0			1.0	0.62-5.77	.29	1.0	0.43-2.19	.74	1.0	0.51-2.87	.46
	Local resection	1.22	0.61-3.19	.30	1.91			1.21			1.29		
Margin status	R0	1.0			1.0	1.03-3.28	.05	1.0			1.0		
	R1	1.96	1.28-2.95	.02	1.68			1.58	1.08-2.54	.04	2.10	1.10-3.80	.04
IOERT technical parameters													
IOERT dose (Gy)	<1250	1.0			1.0		.78	1.0			1.0		
	≥1250	0.93	0.51-1.72	.83	0.90	0.45-1.82		1.08	0.65-1.78	.77	0.93	0.55-1.57	.79
IOERT energy (MeV)	<6	1.0			1.0		.71	1.0			1.0		
	≥6	0.87	0.39-1.65	.42	0.82	0.23-2.12		1.10	0.68-1.78	.71	1.42	0.81-2.17	.20
IOERT applicator size (cm)	<9	1.0			1.0		.38	1.0			1.0		
	≥9	0.92	0.39-1.89	.84	0.74	0.38-1.44		0.90	0.46-1.62	.75	0.78	0.47-1.29	.33
Adjuvant treatment													
EBRT treatment to primary tumor	Yes	1.0			1.0	0.31-1.20	.16	1.0	0.44-1.19	.20	1.0	0.31-1.25	.32
	No	0.68	0.38-1.23	.21	0.61			0.72			0.67		
EBRT treatment to LR-STS	Yes	1.0			1.0	1.0-3.61	.05	1.0	0.76-2.16	.36	1.0	0.81-2.45	.31
	No	1.80	1.05-3.17	.04	1.94			1.28			1.49		
EBRT re-irradiation	Yes	1.0			1.0			1.0			1.0		
	No	0.75	0.42-2.01	.55	0.85	0.54-1.74	.73	0.68	0.25-2.09	.71	0.92	0.33-2.32	.88
Adjuvant chemotherapy	Yes	1.0			1.0		.82	1.0			1.0		
	No	1.18	0.50-2.80	.70	1.12	0.43-2.89		1.33	0.71-2.48	.38	1.18	0.41-2.73	.77

Abbreviations: CI = confidence interval; CT = chemotherapy; EBRT = external beam radiation therapy; HR = hazard ratio; LR = local recurrence.

Local control for the study population at 5 and 10 years was 60% and 58% (Fig. 1A). Univariate Cox proportional hazard analyses showed that patients with a time interval from primary tumor diagnosis to local relapse <24 months ($P=.04$), incomplete resection ($P=.02$), high histologic grade ($P=.05$), and no EBRT administered to treat the LR-STS ($P=.04$) were associated with a higher probability of local relapse (Table 3). After adjustment for other covariates, the variables that remained significantly associated with local relapse were no EBRT to the LR-STS ($P=.02$) and R1 margin status ($P=.04$) (Table 4). IOERT in-field control at 5 and 10 years was 73% and 70% (Fig. 1B). Univariate analysis showed that patients with R1 resection ($P=.05$) and no EBRT to treat the LR-STS ($P=.05$) had a higher probability of IOERT in-field relapse (Table 3). In the multivariate analysis, only no EBRT to treat the LR-STS ($P=.03$) retained a significant association with regard to IOERT in-field relapse (Table 4). DFS at 5 and 10 years was 43% and 33% (Fig. 1C). Univariate Cox proportional hazard analysis showed that time interval from primary tumor diagnosis to local relapse <24 months ($P=.01$), high histologic grade ($P=.02$),

Table 4 Factors associated with local control, intraoperative electron beam radiation therapy (IOERT) in-field control, disease-free survival, and overall survival in multivariate analyses

		Local control			IOERT in-field control			Disease-free survival			Overall survival		
Parameter	Variable	HR	95% CI	*P* value	HR	95% CI	*P* value	HR	95% CI	*P* value	HR	95% CI	*P* value
Patient variables													
Time interval from primary to LR (mo)	≥24	-	-	-	-	-	-	1.0			1.0		
	<24							3.87	1.36-7.88	.006	3.44	1.29-7.08	.008
Microscopic surgical specimen													
Histologic grade	1-2	-	-	-	-	-	-	1.0			-	-	-
	3							2.41	1.06-4.92	.04			
Surgery													
Margin status	R0	1.0	1.06-3.34	.04	-	-	-	1.0			1.0		
	R1	1.73						1.72	1.11-2.83	.03	2.41	1.21-4.21	.02
IOERT technical parameters													
CT treatment EBRT treatment to LR-STS	Yes	1.0			1.0			-	-	-	-	-	-
	No	2.12	1.18-3.23	.02	2.08	1.10-3.64	.03						

Abbreviations: CI = confidence interval; CT = chemotherapy; EBRT = external beam radiation therapy; HR = hazard ratio.

and R1 resection status ($P=.04$) were associated with a higher probability of metastasis (Table 3). After adjustment for other covariates, primary tumor diagnosis to local relapse <24 months ($P=.006$), high histologic grade ($P=.04$), and incomplete margin status ($P=.03$) retained a significant association with DFS (Table 4). Overall survival at 5 and 10 years was 52% and 33% (Fig. 1D). In the univariate analysis, patients with age ≥50 years ($P=.05$), a time interval from primary tumor diagnosis to local relapse <24 months ($P=.01$), and an R1 margin status ($P=.04$) were at a significantly higher risk of death (Table 3). Multivariate analysis showed that only R1 margin status ($P=.02$) and primary tumor diagnosis to local relapse <24 months ($P=.006$) were significantly associated with OS (Table 4).

Overall, 16 patients (16%) had grade ≥3 acute toxicity (severe skin reactions [n=7, grade 3] and wound-healing disorders [n=5, grade 3; n=4, grade 4]). Severe skin reactions and wound-healing disorders were more frequently observed in patients with extremity LR-STS (n=3, grade 3) and trunk wall LR-STS (n=2, grade 3; n=2, grade 4), respectively. Thirteen patients (13%) developed chronic toxicity ≥3 (neuropathy [n=6, grade 3], necrosis/fistula/ulcer [n=3, grade 3], and severe chronic lymphedema [n=7, grade 3]). Neuropathy, necrosis/fistula/ulcer and severe chronic lymphedema were more frequently observed in patients with retroperitoneal LR-STS (n=3, grade 3), trunk wall LR-STS (n=2, grade 3) and extremity LR-STS (n=7, grade 3), respectively. No significant differences were observed in acute or chronic toxicity between patients who received EBRT to treat the local relapse and those who did not. No perioperative deaths or deaths related to long-term treatment were recorded.

Discussion

To our knowledge, this is the first study to focus on long-term outcomes in patients with LR-STS treated with IOERT, surgical resection, and EBRT. Our most relevant findings can be summarized as follows. First, we observed that not combining EBRT with surgical resection and IOERT in patients with LR-STS was significantly associated with an increased probability of LR and IOERT in-field relapse. Second, we found that patients with a time interval <24 months between primary tumor diagnosis and local relapse had an increased probability of overall metastasis and death. Finally, patients with microscopically positive margins had worse overall outcomes.

Several expert IOERT institutions with broad inclusion criteria (primary advanced and locally recurrent) and mixed cohorts of extremity, trunk wall, and retroperitoneal sarcomas have reported results comparable to those in the present analysis (Table 5). The present retrospective single-center analysis included only patients with LR-STS. Selection was not based on primary site, volume of tumor recurrence, or modalities of initial treatment. All patients had close margins (<1 cm) or positive margins (R1), features related to difficult surgical resection and adverse prognosis (3).

Discrimination between primary advanced and LR-STS in IOERT-based studies is important, because worse overall outcomes are consistently described for LR-STS (5, 6). Several groups have successfully implemented and reported combined management (IORT and surgical resection) in mixed cohorts for patients with primary and LR-STS (5-year local control [60%-80%]) (11-13).

Although it is widely accepted that the quality of the surgical margin is of paramount importance for local control, what constitutes adequate surgical margins is not well established. Positive surgical margins have been consistently reported as an adverse prognostic factor for local control (12, 13). Oertel et al (12) reported high 5-year local control (78%) and OS (77%) in the largest single-institution experience reported to date (n=153), in which IOERT combined with moderate doses of EBRT for the management of extremity STS (32% recurrent). Local control was more favorable for patients with complete margin resection (5-year locoregional control 85% vs 60%, $P=.03$). Azinovic et al (13) analyzed 45 patients with extremity sarcomas (42% recurrent

Table 5 Series reporting long-term outcomes for patients with soft tissue sarcomas

	N	Median follow-up (mo)	IORT	Disease status		(Neo) Adjuvant EBRT	Neo (Adjuvant) CT	5-year local Kaplan-Meier estimate			
				Primary	Recurrent			IOERT in-field LC	LC	DFS	OS
Zagars et al*	1225	114#	<1%	84%	16%	100%	33%	NR	83%	60%	71%§
DeLaney et al*	154	75	10%	87%	13%	100%	15%	NR	76%	47%	65%
Alektiar et al†	32	33	100%	37%	63%	78%	13%	NR	62%	82%	55%§
Petersen et al†	87	42	100%	49%	51%	89%	12%	NR	59%	55%	29%§
Dziewieski et al†	46	20	100%	13%	87%	52%	4%	NR	51%	NR	NR
Krempien et al†	67	30	100%	39%	61%	67%	NR	72%	40%	50%‖	28%§
Tran et al*	50	59	100%	30%	70%	37%	32%	55%	26%	51%‖	25%§
Azinovic et al‡	45	93#	100%	74%	26%	80%	73%	NR	80%¶	56%¶	NR
Oertel et al‡	153	33	100%	62%	38%	62%	NR	NR	78%	48%‖	77%

Abbreviations: CT = chemotherapy; DFS = disease-free survival; EBRT = external beam radiation therapy; IORT = intraoperative radiation therapy; LC = local control; OS = overall survival.

* Mixed cohorts (retroperitoneum, pelvis, extremity, head-and-neck, and/or trunk wall).

† Retroperitoneal soft tissue sarcoma only.

‡ Extremity soft tissue sarcoma only.

§ Disease-specific survival.

‖ Distant metastasis-free survival.

¶ Crude rates.

Median follow-up for surviving patients.

tumors) treated with moderate-dose postoperative EBRT (45-50 Gy) and IOERT. Five-year local control was 87%, and margin status (negative or close margins vs positive margins [$P = .04$]) significantly affected local control. In the current analysis, positive microscopic resection margins were significantly associated with poor overall outcomes in the multivariate analysis. Nonetheless, to compare results from different institutional experiences and to evaluate the effect of different treatment modalities on local control, a strict definition of the margin assessment procedure is required. Several routines for margin assessment have been described (16). Most studies report that the margin is assessed by the surgeon and validated by the pathologist or jointly assessed by both. The surgeon can measure the thickness of the closest margin of surrounding tissue on the fresh specimen, omitting areas of shortest distances where there is fascial involvement. The pathologist can measure the thickness of the tumor macroscopically on fresh or formalin-fixed specimen using several slices. In recent years, reports on the surgical margin have generally been accompanied by the microscopic tumor tissue location at the specimen perimeter (17). Finally, the shortest distance without fascial coverage can be measured microscopically as the distance from tumor tissue to an inked surface (16). Interpretation of these anatomical and histological features is even more uncertain in postresection and irradiated sarcoma specimens. In the present analysis, the pathologist defined a positive margin during surgery using frozen section analysis.

Histological grade is an independent predictive factor for development of metastasis in most cases of adult STS (4). Not surprisingly, therefore, grade was also an independent prognostic factor for DFS in the present analysis. Intensified local treatment needs to be tested in the context of more efficient concurrent, neoadjuvant, and adjuvant systemic therapy. Although the effect of adjuvant chemotherapy on survival for resected STS has yet to be established (18), distant metastases remain the dominant pattern of progression for high-risk extremity STS (3).

We acknowledge several limitations of our study. First, the treated population (103 patients treated over 26 years) was heterogeneous, receiving different treatment combinations, sequences, and doses. Radiation therapy technology and consensus on gross tumor volume and clinical target volume has also changed over time (19). Second, we included extremity, trunk, and retroperitoneal STS together, although it is currently recognized that there are very specific and unique anatomical challenges relating to the management of recurrence in each of these sites, and for the retroperitoneal site at least, there may be biologic differences in behavior and prognosis (3). The fact that anatomic site was not a significant predictor of overall outcomes is likely a reflection of a number limitation of our clinical data. Finally, it is very difficult to assess the specific contribution of the IOERT treatment component, because this analysis cannot compare local sarcoma control with or without intraoperative electron irradiation. Locally recurrent STS (oligorecurrence) is a broad disease category comprising several types of patients and tumors (20). Oligorecurrence involves a restricted locoregional tumor burden and has been proposed as a common criterion for treatment strategy optimization (20). Intraoperative radiation therapy is an attractive method of dose escalation for LR-STS with close or positive margins (5). IORT has several advantages over EBRT, such as more precise delivery of radiation to a surgically identified high-risk area, mobilization of dose-sensitive organs at risk, temporarily out of the radiation boost field, and shortening of overall treatment time (dose-dense radiation therapy). As reported by Azinovic et al (13), patients receiving adjuvant EBRT in the current analysis had a higher local control rate than patients in whom EBRT was omitted (85% vs 74%). Even more, we observed that not receiving EBRT for the local relapse was associated with an increased likelihood of IOERT in-field relapse. Although most LR-STS tumors recurred within the IOERT field (69%), in the present analysis a higher IOERT dose did not improve local control. Novel technologies could potentially make IOERT

considerations more influential, especially in an attempt to induce immune stimulation against sarcomas (21).

Treatment-related toxicity, including that induced by IOERT administered to treat LR-STS, was well tolerated by our 103 patients. The low rate of severe toxic events suggests that a multimodality approach with re-resection and IOERT is feasible without prohibitive long-term side effects. Location-associated risk should be carefully assessed during IOERT administration to minimize the irradiated volume. The definition of organs at risk, availability of dose−volume histograms, and estimations of 3D dose distribution play a key role in optimization of IOERT (14). Detailed planning on the part of the surgeon and radiation oncologist, along with detailed input from the radiologist before surgery and from the pathologist at the time of resection, is decisive for dose-escalation strategies within the tumor bed (field-within-field technique). Future clinical research should focus on functional outcome and quality of life.

References

1. Haas RL, Delaney TF, O'Sullivan B. Radiotherapy for management of extremity soft tissue sarcomas: Why, when, and where? *Int J Radiat Oncol Biol Phys* 2012;84:572-580.
2. LeVay J, O'Sullivan B, Catton C, et al. Outcome and prognostic factors in soft tissue sarcoma in the adult. *Int J Radiat Oncol Biol Phys* 1993;27:1091-1099.
3. Delaney TF, Kepka L, Goldberg SI, et al. Radiation therapy for control of soft-tissue sarcomas resected with positive margins. *Int J Radiat Oncol Biol Phys* 2007;67:1460-1469.
4. Zagars GK, Ballo MT, Pisters PW, et al. Prognostic factors for patients with localized soft-tissue sarcoma treated with conservation surgery and radiation therapy: An analysis of 1225 patients. *Cancer* 2003;97:2530-2543.
5. Petersen IA, Krempien R, Beauchamp C, et al. Extremity and trunk soft-tissue sarcomas. In: Gunderson LL, Willet CG, Calvo FA, Harrison LB, editors. Intraoperative Irradiation Techniques and Results. Current Clinical Oncology. 2nd edition. New York: Humana Press, Springer; 2011. p. 387-405.
6. Alektiar KM, Hu K, Anderson L, et al. High-dose-rate intraoperative radiation therapy (HDR-IORT) for retroperitoneal sarcomas. *Int J Radiat Oncol Biol Phys* 2000;47:157-163.
7. Petersen IA, Haddock MG, Donohue JH, et al. Use of intraoperative electron beam radiotherapy in the management of retroperitoneal soft tissue sarcomas. *Int J Radiat Oncol Biol Phys* 2002;52:469-475.
8. Krempien R, Roeder F, Oertel S, et al. Intraoperative electron beam therapy for primary and recurrent retroperitoneal soft-tissue sarcoma. *Int J Radiat Oncol Biol Phys* 2006;65:773-779.
9. Dziewirski W, Rutkowski P, Nowecki ZI, et al. Surgery combined with intraoperative brachytherapy in the treatment of retroperitoneal sarcomas. *Ann Surg Oncol* 2006;13:245-252.
10. Tran PT, Hara W, Su Z, et al. Intraoperative radiation therapy for locally advanced and recurrent soft-tissue sarcomas in adults. *Int J Radiation Oncology Biol Phys* 2008;72:1146-1153.
11. Haddock MG, Petersen IA, Pritchard D, et al. IORT in the management of extremity and limb girdle soft tissue sarcomas. *Front Radiat Ther Oncol* 1997;31:151-152.
12. Oertel S, Treiber M, Zahlten-Hinguranage A, et al. Intraoperative electron boost radiation followed by moderate doses of external beam radiotherapy in limb-sparing treatment of patients with extremity soft-tissue sarcoma. *Int J Radiat Oncol Biol Phys* 2006;64:1416-1423.
13. Azinovic I, Martinez Monge R, Javier Aristu J, et al. Intraoperative radiotherapy electron boost followed by moderate doses of external beam radiotherapy in resected soft-tissue sarcoma of the extremities. *Radiother Oncol* 2003;67:331-337.
14. Pascau J, Santos Miranda JA, Calvo FA, et al. An innovative tool for intraoperative electron beam radiotherapy simulation and planning: Description and initial evaluation by radiation oncologists. *Int J Radiat Oncol Biol Phys* 2012;83:287-295.
15. Cox JD, Stetz J, Pajak TF. Toxicity criteria of the Radiation Oncology Group (RTOG) and the European Organization for Research and Treatment of Cancer (EORTC). *Int J Radiat Oncol Biol Phys* 1995;31:1341-1346.
16. Sampo M, Tarkkanen M, Huuhtanen R, et al. Impact of the smallest surgical margin on local control in soft tissue sarcoma. *Br J Surg* 2008;95:237-243.
17. Kawaguchi N, Matumoto S, Manabe J. New method of evaluating the surgical margin and safety margin for musculoskeletal sarcoma, analysed on the basis of 457 surgical cases. *J Cancer Res Clin Oncol* 1995;121:555-563.
18. Pervaiz N, Colterjohn N, Farrokhyar F, et al. A systematic meta-analysis of randomized controlled trials of adjuvant chemotherapy for localized resectable soft-tissue sarcoma. *Cancer* 2008;113:573-581.
19. Rimner A, Brennan MF, Zhang Z, et al. Influence of compartmental involvement on the patterns of morbidity in soft tissue sarcoma of the thigh. *Cancer* 2009;115:149-157.
20. Weichselbaum RR, Hellman S. Oligometastases revisited. *Nat Rev Clin Oncol* 2011;8:378-382.
21. Wang D, Bosch W, Roberge D, et al. RTOG sarcoma radiation oncologists reach consensus on gross tumor volume and clinical target volume on computed tomographic images for preoperative radiotherapy of primary soft tissue sarcoma of extremity in Radiation Therapy Oncology Group studies. *Int J Radiat Oncol Biol Phys* 2011;81:525-528.
22. Finkelstein SE, Iclozan C, Bui MM, et al. Combination of external beam radiotherapy (EBRT) with intratumoral injection of dendritic cells as neo-adjuvant treatment of high-risk soft tissue sarcoma patients. *Int J Radiat Oncol Biol Phys* 2012;82:924-932.

ELSEVIER LICENSE
TERMS AND CONDITIONS

Dec 16, 2013

This is a License Agreement between Claudio V Sole ("You") and Elsevier ("Elsevier") provided by Copyright Clearance Center ("CCC"). The license consists of your order details, the terms and conditions provided by Elsevier, and the payment terms and conditions.

All payments must be made in full to CCC. For payment instructions, please see information listed at the bottom of this form.

Supplier	Elsevier Limited The Boulevard,Langford Lane Kidlington,Oxford,OX5 1GB,UK
Registered Company Number	1982084
Customer name	Claudio V Sole
Customer address	Americo Vespucio norte 1314 Santiago, 7603360
License number	3290680306290
License date	Dec 16, 2013
Licensed content publisher	Elsevier
Licensed content publication	International Journal of Radiation Oncology*Biology*Physics
Licensed content title	Prognostic Value of External Beam Radiation Therapy in Patients Treated With Surgical Resection and Intraoperative Electron Beam Radiation Therapy for Locally Recurrent Soft Tissue Sarcoma: A Multicentric Long-Term Outcome Analysis
Licensed content author	Felipe A. Calvo,Claudio V. Sole,Mauricio Cambeiro,Angel Montero,Alfredo Polo,Carmen Gonzalez,Miguel Cuervo,Mikel San Julian,Jose L. Garcia-Sabrido,Rafael Martinez-Monge
Licensed content date	1 January 2014
Licensed content volume number	88
Licensed content issue number	1
Number of pages	8
Start Page	143
End Page	150
Type of Use	reuse in a thesis/dissertation
Intended publisher of new work	other
Portion	full article
Format	both print and electronic
Are you the author of this Elsevier article?	Yes

Will you be translating?	No
Title of your thesis/dissertation	Valor Pronóstico de la Radioterapia Externa en el Tratamiento Multidisciplinario de Pacientes con Oligorecurrencia Locoregional
Expected completion date	Dec 2014
Estimated size (number of pages)	120
Elsevier VAT number	GB 494 6272 12
Permissions price	0.00 USD
VAT/Local Sales Tax	0.00 USD / 0.00 GBP
Total	0.00 USD
Terms and Conditions	

INTRODUCTION

1. The publisher for this copyrighted material is Elsevier. By clicking "accept" in connection with completing this licensing transaction, you agree that the following terms and conditions apply to this transaction (along with the Billing and Payment terms and conditions established by Copyright Clearance Center, Inc. ("CCC"), at the time that you opened your Rightslink account and that are available at any time at http://myaccount.copyright.com).

GENERAL TERMS

2. Elsevier hereby grants you permission to reproduce the aforementioned material subject to the terms and conditions indicated.

3. Acknowledgement: If any part of the material to be used (for example, figures) has appeared in our publication with credit or acknowledgement to another source, permission must also be sought from that source. If such permission is not obtained then that material may not be included in your publication/copies. Suitable acknowledgement to the source must be made, either as a footnote or in a reference list at the end of your publication, as follows:

“Reprinted from Publication title, Vol /edition number, Author(s), Title of article / title of chapter, Pages No., Copyright (Year), with permission from Elsevier [OR APPLICABLE SOCIETY COPYRIGHT OWNER].” Also Lancet special credit - “Reprinted from The Lancet, Vol. number, Author(s), Title of article, Pages No., Copyright (Year), with permission from Elsevier.”

4. Reproduction of this material is confined to the purpose and/or media for which permission is hereby given.

5. Altering/Modifying Material: Not Permitted. However figures and illustrations may be altered/adapted minimally to serve your work. Any other abbreviations, additions, deletions and/or any other alterations shall be made only with prior written authorization of Elsevier Ltd. (Please contact Elsevier at permissions@elsevier.com)

6. If the permission fee for the requested use of our material is waived in this instance, please be advised that your future requests for Elsevier materials may attract a fee.

7. Reservation of Rights: Publisher reserves all rights not specifically granted in the combination of (i) the license details provided by you and accepted in the course of this licensing transaction, (ii) these terms and conditions and (iii) CCC's Billing and Payment terms and conditions.

8. License Contingent Upon Payment: While you may exercise the rights licensed immediately upon issuance of the license at the end of the licensing process for the transaction, provided that you have disclosed complete and accurate details of your proposed use, no license is finally effective unless and until full payment is received from you (either by publisher or by CCC) as provided in CCC's Billing and Payment terms and conditions. If full payment is not received on a timely basis, then any license preliminarily granted shall be deemed automatically revoked and shall be void as if never granted. Further, in the event that you breach any of these terms and conditions or any of CCC's Billing and Payment terms and conditions, the license is automatically revoked and shall be void as if never granted. Use of materials as described in a revoked license, as well as any use of the materials beyond the scope of an unrevoked license, may constitute copyright infringement and publisher reserves the right to take any and all action to protect its copyright in the materials.

9. Warranties: Publisher makes no representations or warranties with respect to the licensed material.

10. Indemnity: You hereby indemnify and agree to hold harmless publisher and CCC, and their respective officers, directors, employees and agents, from and against any and all claims arising out of your use of the licensed material other than as specifically authorized pursuant to this license.

11. No Transfer of License: This license is personal to you and may not be sublicensed, assigned, or transferred by you to any other person without publisher's written permission.

12. No Amendment Except in Writing: This license may not be amended except in a writing signed by both parties (or, in the case of publisher, by CCC on publisher's behalf).

13. Objection to Contrary Terms: Publisher hereby objects to any terms contained in any purchase order, acknowledgment, check endorsement or other writing prepared by you, which terms are inconsistent with these terms and conditions or CCC's Billing and Payment terms and conditions. These terms and conditions, together with CCC's Billing and Payment terms and conditions (which are incorporated herein), comprise the entire agreement between you and publisher (and CCC) concerning this licensing transaction. In the event of any conflict between your obligations established by these terms and conditions and those established by CCC's Billing and Payment terms and conditions, these terms and conditions shall control.

14. Revocation: Elsevier or Copyright Clearance Center may deny the permissions described in this License at their sole discretion, for any reason or no reason, with a full refund payable to you. Notice of such denial will be made using the contact information provided by you. Failure to receive such notice will not alter or invalidate the denial. In no event will Elsevier or Copyright Clearance Center be responsible or liable for any costs, expenses or damage incurred by you as a result of a denial of your permission request, other than a refund of the amount(s) paid by you to Elsevier and/or Copyright Clearance Center for denied permissions.

LIMITED LICENSE

The following terms and conditions apply only to specific license types:

15. **Translation**: This permission is granted for non-exclusive world **English** rights only unless your license was granted for translation rights. If you licensed translation rights you may only translate this content into the languages you requested. A professional translator

must perform all translations and reproduce the content word for word preserving the integrity of the article. If this license is to re-use 1 or 2 figures then permission is granted for non-exclusive world rights in all languages.

16. **Website**: The following terms and conditions apply to electronic reserve and author websites:
Electronic reserve: If licensed material is to be posted to website, the web site is to be password-protected and made available only to bona fide students registered on a relevant course if:
This license was made in connection with a course,
This permission is granted for 1 year only. You may obtain a license for future website posting,
All content posted to the web site must maintain the copyright information line on the bottom of each image,
A hyper-text must be included to the Homepage of the journal from which you are licensing at http://www.sciencedirect.com/science/journal/xxxxx or the Elsevier homepage for books at http://www.elsevier.com , and
Central Storage: This license does not include permission for a scanned version of the material to be stored in a central repository such as that provided by Heron/XanEdu.

17. **Author website** for journals with the following additional clauses:

All content posted to the web site must maintain the copyright information line on the bottom of each image, and the permission granted is limited to the personal version of your paper. You are not allowed to download and post the published electronic version of your article (whether PDF or HTML, proof or final version), nor may you scan the printed edition to create an electronic version. A hyper-text must be included to the Homepage of the journal from which you are licensing at http://www.sciencedirect.com/science/journal/xxxxx . As part of our normal production process, you will receive an e-mail notice when your article appears on Elsevier's online service ScienceDirect (www.sciencedirect.com). That e-mail will include the article's Digital Object Identifier (DOI). This number provides the electronic link to the published article and should be included in the posting of your personal version. We ask that you wait until you receive this e-mail and have the DOI to do any posting.

Central Storage: This license does not include permission for a scanned version of the material to be stored in a central repository such as that provided by Heron/XanEdu.

18. **Author website** for books with the following additional clauses:
Authors are permitted to place a brief summary of their work online only.
A hyper-text must be included to the Elsevier homepage at http://www.elsevier.com . All content posted to the web site must maintain the copyright information line on the bottom of each image. You are not allowed to download and post the published electronic version of your chapter, nor may you scan the printed edition to create an electronic version.

Central Storage: This license does not include permission for a scanned version of the material to be stored in a central repository such as that provided by Heron/XanEdu.

19. **Website** (regular and for author): A hyper-text must be included to the Homepage of the journal from which you are licensing at http://www.sciencedirect.com/science/journal/xxxxx. or for books to the Elsevier homepage at http://www.elsevier.com

20. **Thesis/Dissertation**: If your license is for use in a thesis/dissertation your thesis may be submitted to your institution in either print or electronic form. Should your thesis be

published commercially, please reapply for permission. These requirements include permission for the Library and Archives of Canada to supply single copies, on demand, of the complete thesis and include permission for UMI to supply single copies, on demand, of the complete thesis. Should your thesis be published commercially, please reapply for permission.

21. **Other Conditions**:

v1.6

If you would like to pay for this license now, please remit this license along with your payment made payable to "COPYRIGHT CLEARANCE CENTER" otherwise you will be invoiced within 48 hours of the license date. Payment should be in the form of a check or money order referencing your account number and this invoice number RLNK501182767.
Once you receive your invoice for this order, you may pay your invoice by credit card. Please follow instructions provided at that time.

Make Payment To:
Copyright Clearance Center
Dept 001
P.O. Box 843006
Boston, MA 02284-3006

For suggestions or comments regarding this order, contact RightsLink Customer Support: customercare@copyright.com or +1-877-622-5543 (toll free in the US) or +1-978-646-2777.

Gratis licenses (referencing $0 in the Total field) are free. Please retain this printable license for your reference. No payment is required.

Informe del Director de la Tesis Doctoral

DATOS DE LA TESIS DOCTORAL	
Nombre del Doctorando	*CLAUDIO VICENTE SOLE PESUTIC*
Título de la Tesis	*VALOR PRONÓSTICO DE LA RADIOTERAPIA EXTERNA EN EL TRATAMIENTO MULTIDISCIPLINARIO DE PACIENTES CON OLIGO-RECURRENCIA LOCO-REGIONAL*
Facultad o Centro	*FACULTAD DE MEDICINA*

DATOS DEL DIRECTOR DE LA TESIS DOCTORAL	
Nombre Completo	*FELIPE ANGEL CALVO MANUEL*
Centro al que pertenece y dirección	*Departamento de Radiología y Medicina Física (Facultad Medicina) Departamento de Oncología. Hospital General Universitario Gregorio Marañon*
D.N.I/Pasaporte	*00661639 K*
e-mail	*fcalvo.hgugm@salud.madrid.org*

	VALORACIÓN DE LA TESIS			
	Muy Buena	*Buena*	*Suficiente*	*Deficiente*
Originalidad	*x*			
Definición Objetivos	*x*			
Metodología	*x*			
Relevancia Resultados	*x*			
Discusión / Conclusiones	*x*			

INFORME *(en caso necesario se podrán añadir más hojas):*

Se trata de un trabajo de investigación que analiza retrospectivamente (sobre registro prospectivo de datos institucionales) los aspectos metodológicos, diagnósticos y terapéuticos involucrados en el abordaje de una nueva categoría de patrón evolutivo en cáncer humano definido como enfermedad oligo-recurrente loco-regional. La identificación de esta entidad clínico evolutiva de "oligo-cáncer (oligo-metástasis y oligo-recurrencias)" solo ha sido posible mediante el análisis de experiencias clínicas con abordaje homogéneo en el recate de recidivas oligotópicas. Esta línea de actividad (sistematización del rescate oncológico) se concentra en instituciones con programas de oncología multidisciplinar estrechamente coordinados, tradición quirúrgica experta y tecnología radioterápica avanzada y adaptada a metodologías de intensificación radio-quirúrgica loco-regional, en particular programas de radioterapia intraoperatoria.

En este contexto se han evaluado los elementos asociados al pronóstico oncológico evolutivo en un extenso grupo de pacientes (se trata de la experiencia clínica mas madura en tiempo de seguimiento, con mayor numero de enfermos analizados y mayor diversidad de subtipos histológicos y localizaciones iniciales del tumor primario, salvo la experiencia de la Clínica Mayo en cáncer colo-rectal recurrente; en el caso de los sarcomas de partes blandas es la primera experiencia multi-institucional que se comunica internacionalmente con metodología de "pooled-analysis").

Mediante el registro en base de datos de mas de 40 variables individualizadas por paciente con información clínico-terapéutica-evolutiva (1985 a 2010), agrupando las cohortes de pacientes en recurrencias de origen en cáncer rectal (60), ginecológico (61) y sarcomas de partes blandas (103), se ha realizado un análisis uni y multivariente de factores potencialmente asociados al pronóstico oncológico, con un énfasis especial en los resultados observados en control loco-regional (objetivo dominante en los programas de intensificación terapéutica con modalidades locales de tratamiento, como son la cirugía y radioterapia de rescate). La hipótesis explorada es confirmar (es una hipótesis aceptada en modelos de cáncer localmente avanzado primario) que el control local tumoral está influido por la intensidad terapéutica integral en abordajes multidisciplinares que combinan cirugía de máximo esfuerzo, radioterapia intraoperatoria y radioterapia externa en el rescate de cáncer oligo-recurrente en los modelos de subtipos de enfermedad descritos.

Los resultados categóricos que se identifican en el análisis realizado pueden resumirse en:

1. ***El cáncer oligo-recurrente es una entidad oncológica reconocible en la practica clínica diaria. Admite rescate radical multimodal que generan pacientes vivos a largo plazo, sin evidencia de cáncer, en todas las categorías de adversidad oncológica pronostica evaluadas.***

2. ***El control local esta relacionado con la intensidad terapéutica integral. Especialmente la asociación de un componente de radioterapia externa fraccionada convencional impacta favorablemente en el pronóstico.***

3. ***En los modelos de cáncer de recto y sarcomas el tratamiento local intensivo compensa la adversidad local asociada a la fragmentación del espécimen quirúrgico y/o la reseción incompleta con persistencia de enfermedad probada (R1). Este dato no se ha descrito previamente.***

Este trabajo ha sido elaborado con el formato de la normativa que regula la competencia por obtener la mención de Diploma Europeo. Los revisores internacionales han sido el Prof. Marco Krengli (Catedrático de Oncología Radioterápica de la Universidad de Novara y coordinador del European Registry y President- Elect de la International Society of Intraoperative Radiation Therapy) y el Prof. Vincenzo Valentini (Catedrático de Radioterapia, Instituto de Radiología, Universidad Católica dei Sacro Cuore, Policlinico Gemeli y Presidente de la European Society for Therapeutic Radiology and Oncology). Los manuscritos que sustentan la solicitud para optar al Diploma Europeo están publicados en revistas científicas del primer cuartil de su área de conocimiento (Radiology, también Oncology): International Journal of Radiation Oncology Biology and Physics (FI 4,524) y Strahlenther und Onkolgie (FI 4,163).

Finalmente, deseo hacer una reflexión personal que no he incluido nunca en informes precedentes como director de tesis doctorales. Tanto el trabajo realizado, como la colaboración con el doctorando, los considero elementos de enorme provecho y satisfacción académica. He aprendido del talento de mi doctorando lecciones de creatividad en la interpretación de la información y búsqueda de nuevos retos en el análisis de datos. Me ha conmovido comprobar, en la visión panorámica del análisis de datos que contiene este estudio, el trabajo esforzado, generoso y compasivo, meticuloso y técnicamente admirable de mis compañeros del Hospital General Universitario Gregorio Marañón, que con una práctica clínica esmerada y un sentido de innovación en la enfermedad oncológica difícilmente curable, han generado los mimbres asistenciales para impulsar conocimiento valioso en el contexto de una actividad exigente y compleja hospitalaria, explorando las fronteras de la oncología personalizada. Ninguna nueva propuesta de Tesis Doctoral es "otra Tesis Doctoral más"… Ésta, lo es menos…

Madrid, a 4 de Junio de 2014

Fdo.:Felipe A. Calvo Manuel

Este impreso deberá entregarse al Departamento/Órgano responsable del Posgrado/ Comisión responsable del Programa de Doctorado, para su estudio y aprobación en la admisión a trámite de la tesis doctoral. Asimismo, deberá incluirse entre la documentación enviada a la Comisión de Doctorado para la designación del Tribunal y aprobación de la defensa de la Tesis Doctoral.